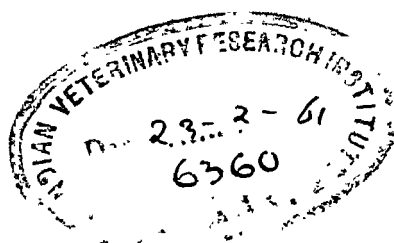


**RECENT ADVANCES
IN NEUROLOGY AND
NEUROPSYCHIATRY**



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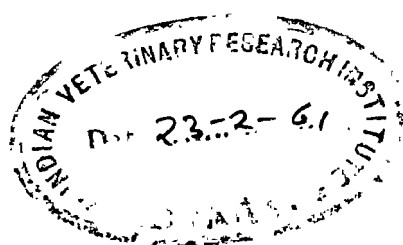
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RECENT ADVANCES IN NEUROLOGY AND NEUROPSYCHIATRY

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SIXTH EDITION

With 43 Illustrations



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PREFACE TO THE SIXTH EDITION

THIS book has been entirely rewritten since the last edition, and in order to keep up with the increasing degree of specialisation within neurology we have asked Dr. Denis Hill to contribute a chapter on electro-encephalography and Dr. David Sutton one on neuroradiology, while Mr. Northfield again deals with the surgical aspect of the subject. Progress in neurology continues to justify the inclusion of neuropsychiatry in such a book as this, for in neurophysiology, electro-encephalography, clinical neurology and neurosurgery the common ground between neurology and psychiatry increases in importance. We are grateful to Dr. Harry May for his advice on the section dealing with the chemotherapy of meningitis and to Dr. Peter Croft for his help with the index.

W. R. B.

E. B. S.

PREFACE TO THE FIRST EDITION

IF a "genealogical table" of the Sciences were to be drawn up, it would effectively demonstrate the intimate connections of neurology with every branch of "Natural Philosophy" which derives directly from the science of Biology.

It is instructive to turn to any text-book of physiology and reckon what a preponderating proportion of its pages is devoted to the study of the nervous system; and the same applies to text-books of anatomy, embryology, pathology and general medicine.

The relationship existing between neurology and psychology should be even more apparent. The study of psychological problems without an adequate knowledge of the physiology and pathology of the central nervous system can be likened to the exploration of uncharted seas without the aid of a compass; and yet there are many psychologists who undertake the rash venture.

Recent research has but enhanced the indebtedness to neurology of other departments of knowledge. Psychology as yet has hardly begun to assimilate Pavlov's remarkable studies of the conditioned reflex; but it is already clear that he has provided the key to many problems of both normal and abnormal mental processes. General medicine owes to neurology, and in particular to neurosurgery, almost the whole of its knowledge of the pituitary gland, and recent investigations of the tuber cinereum indicate that the nervous system acts as an unsuspected integrator of many metabolic and endocrine functions. Bacteriology has found in the susceptibility of the nervous system to infection with filterable viruses a great incentive to the study of these pathogenic agents. Ophthalmology owes to neurology, if not the original use of the ophthalmoscope and the perimeter, at least many of their most important applications. Lastly, biology is only now beginning to appreciate the contribution which the comparative study of posture in reference to its disorders in man may bring to the solution of evolutionary problems. All these aspects of neurology find some reflection in this book.

It has been our object in this book to collect and collate the most important neurological contributions of recent years and to treat our material in such a way that fundamental principles

emerge from a wealth of detail. It is not for us to say whether or no we have succeeded; but we can confidently assert that the book contains matter of direct concern to the student of medicine, physiology, therapeutics, pathology and (indirectly) psychology.

The importance accorded to methods of treatment in our *résumé* of recent advances in neurology may possibly do something towards removing the sting from the criticism that the neurologist can diagnose, but not treat; that neurology is an admirable academic pastime, but of little use to the sufferer from nervous diseases. This reproach is refuted merely by the steady progress of neurosurgery. For not only has the operative mortality of intracranial tumour fallen, until in the most skilled hands it is now less than 10 per cent., but by a more and more radical technique it is proving possible to remove an increasingly large number of tumours. Thus the accurate localisation of an intracranial tumour, once of little more than academic interest, is now a problem of urgent practical importance, upon the correct solution of which the patient's life may depend.

A book such as ours can, of course, make no claim to be comprehensive; it must of its nature be selective. There were a great many factors determining our selection of material from the great wealth of valuable neurological work presented to our choice. Chief among these was the intention that all the subjects treated should have a clinical bearing; in other words, that the book should be an auxiliary text-book of *applied* neurology.

We hope in this way to be able to meet the needs of the medical student, the qualified student of medicine reading for higher examinations, and the practitioner of general medicine, as well as to interest the student whose studies have a less direct application.

It is on account of this clinical bias that so much valuable and important work, such as that of Head on aphasia, Adrian, and Fulton—only to mention three prominent names—is not reviewed in this book. It is to be hoped that in our wish to avoid being stigmatised as “academic” we have not omitted too much of value; in any case, with the limited space at our disposal, many omissions were unavoidable.

We have not described any forms of laboratory technique, partly for the reason that they have been adequately dealt with in other works of recent publication: thus, the various tests

employed in the investigation of the cerebrospinal fluid receive no description in our text. We have, however, appended a table compiled by Dr. Douglas McAlpine, to whom we are indebted for permission to publish, giving the cerebrospinal fluid "pictures" in many common morbid conditions.

The lists of references appended to each chapter will enable the reader to consult the original sources, and should therefore be of value.

We desire to thank Mr. Hugh Cairns for kindly putting at our disposal his expert knowledge of the surgery of the nervous system, and Dr. S. Phillips Bedson for a similar kindly office in respect of the filterable viruses. Neither of these friendly critics is in any way responsible for the opinions expressed in this book. We are also indebted for the loan of illustrations to many friends whose names will be found on the corresponding pages. Finally we should like to express our appreciation of the unfailing courtesy and helpfulness of our publishers.

W. R. B.

E. B. S.

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CHAPTER 1

THE FRONTAL LOBE AND THE ORGANIZATION OF MOVEMENT

DURING recent years the functions of the frontal lobe have been increasingly the subject of research. The operations of neurosurgery have provided material for a re-opening of the question of the part played by the frontal lobes in mental life. Experimental physiology has brought to the fore the problem of whether the precentral and the premotor areas differ in function, and whether differences in the clinical pictures of motor disorder can be correlated with lesions in these two situations. Exploration of the orbital surface suggests that some parts of this area may be concerned in the regulation of important autonomic functions and the anterior part of the cingulate gyrus has been found to be not only an important suppressor zone, but also related to the emotional life. Before discussing these questions it is necessary to consider the anatomical basis of the subdivisions of the frontal lobes.

Cyto-Architectonic Subdivisions

Campbell first proposed a division of the frontal lobe into separate areas; and Campbell's scheme was subsequently modified by Brodmann. The basis of the distinction was differences in the histological structure of the cortex in different areas. Brodmann's areas figure in all subsequent work and must therefore be described in some detail.

Brodmann's Area 4 (Motor Area). This area is characterized by the presence of the giant pyramidal cells of Betz in layer 5. Area 4 begins in the depths of the central sulcus and in man it is almost entirely concealed within this, extending on to the rostral lip of the sulcus only in its lower part. Area 4 is subdivided into superior, middle and inferior parts known as 4a, the leg area, 4b, the arm area, and 4c, the face area, respectively.

Area 6 (Premotor). Area 6 is histologically similar to area 4 except for the absence of the giant pyramidal cells of Betz in the fifth layer. Area 6 lies anteriorly to area 4. Its posterior boundary is the anterior boundary of area 4, and it extends forward on the precentral convolution. Like area 4, area 6 is also subdivided,

the more important divisions being area 6a α , which lies superiorly, and area 6a β , which lies inferiorly and the lower part of which constitutes Broca's area.

Area 8 (Frontal Eye Field). The posterior part of the second frontal convolution, Brodmann's area 8, is the frontal cortical centre for movements of the eyes.

Areas 9, 10, 11 and 12 (Prefrontal Area). The part of the frontal lobe lying anteriorly to areas 6 and 8 is known as the prefrontal area, or sometimes as the "frontal association areas". In cellular structure this area differs strikingly from areas 4 and 6, the motor cells both large and small being virtually absent from the fifth layer.

The Orbital Surface. Walker (1940) has made a cyto-architectural map of the frontal areas of the macaque to which he has applied numerical designations derived from Brodmann's designations of comparable areas in the human cerebral cortex. Recent experimental workers on this part of the brain have employed Walker's numbering.

The Cingulate Gyrus. The anterior part of the cingulate gyrus is numbered area 24 by both Brodmann and Walker.

The Rôle of the Frontal Lobe in Voluntary Movement

The reader who attempts to form a clear picture of the organization of voluntary movement in the nervous system from the papers on this subject published during the last twenty years is likely to end his reading in a state of bewilderment. His confusion may result not only from the wide variety of methods of investigation employed, but even more from the fact that experts of equal eminence in their respective fields appear to have drawn opposite and irreconcilable theoretical conclusions from the observations which have been made. The literature on this subject is now so vast that any comprehensive review of it within the space available is quite impossible. All that will be attempted in this chapter is to give examples to illustrate the different methods employed and the different conclusions which have been drawn from them and to see whether the conflicting views can to any extent be reconciled.

The Pyramidal Tract

Since the pyramidal tract plays such an important part in motor activity it is important that its composition should be defined. It may be noted in passing that the very term pyramidal tract is itself a source of confusion, since its origin as a name

is linked with the pyramids of the medulla and not with the large pyramidal cells of the motor cortex. Lassek (1948) has summarized the results of his investigations into the pyramidal tract. He states that in the area of the pyramids in man there may be in the neighbourhood of a million fibres. About three-fifths of the total possess medullary sheaths. In a biometric analysis of 30,000 pyramidal tract myelinated fibres in two young adults it was shown that 89.6 per cent were 1 to 4 μ in diameter at a level just above the motor decussation; 8.7 per cent were 5 to 10 μ whereas only 1.7 per cent were larger than 10 μ . Over one half of all the fibres measured were approximately 1 μ in thickness. These findings suggest that most of the fibre components are very slow conductors of pyramidal impulses in man and that the majority of the cells of origin should be of small calibre to correspond with the fibre diameters. Lassek and his fellow workers have shown that there are about 34,000 large cells in the cortical area 4, that is, cells between the sizes of 900 to 4,100 square μ . Clearly, therefore, the Betz cells can only be the origin of a very small proportion of the fibres which constitute the pyramidal tract in the medulla. Woolsey and Chang (1948) have sought to throw light on the origins of the pyramidal tracts by stimulating the medullary pyramids of rabbits, cats and monkeys electrically and recording the electrical potential changes produced in the cortex by the arrival of the antidromic volleys thus provoked. The regions of the cortex in which the antidromic potentials were observed in the monkey consisted of areas 8, 6, 4, 3, 1, 2, 5 and 7 of Brodmann. This would suggest that the pyramidal tract arises from wide areas of the cortex including the entire precentral motor cortex as well as the parietal lobes. The whole subject is reviewed by Lassek (1954).

Brodal and Walberg (1952) have made the interesting discovery that the pyramidal tract in the spinal cord contains ascending fibres. Lesions of the spinal cord involving the areas of the lateral or ventral cortico-spinal tracts in the cat produced degenerating fibres in both pyramids and cerebral peduncles, and terminal degeneration was present in the pontine grey matter. Lesions restricted to other areas of the cord did not yield degeneration of that type. The ascending degenerating fibres were distributed equally to the two sides of the brain-stem even with unilateral lesions. The degenerating fibres have been traced to certain areas of the cerebral cortex bilaterally. The motor and sensory areas were studied more particularly and the sensory areas received more

of the ascending pyramidal fibres than the motor. There were indications that other cortical areas also received such fibres. It was estimated that the ascending fibres did not exceed 1/25th of the total number of fibres in the pyramids. The anatomical observations were confirmed by electro-physiological studies showing that after electrical stimulation of cutaneous nerves distinct potentials could be led off from the pyramids, while smaller potentials followed stimulation of muscular nerves. The authors suggest that the ascending fibres in the pyramidal tract may play some part in the plantar and possibly the abdominal reflexes.

The Motor Responses to Cortical Stimulation

Modern electrical methods applied to the stimulation of the cerebral cortex have produced results which are one source of controversy concerning the cortical representation of movement. As an example of one point of view we may take the observations of Ruch, Chang and Ward (1947). The authors point out that all previous investigators have attempted to deduce the representation of muscles by observing the reactions of intact limbs and inferring muscle action from known anatomical arrangements and, to a lesser degree, by observing the activity of individual muscles through the skin. Their method was to isolate the muscles observed in their preparations by freeing them from their insertions and attaching each to a myograph. They then recorded the contractions of the muscles in response to cortical stimulation. They draw the following conclusion from their experiments. "On the basis of the present experimental evidence, it is evident that there exists in the cerebral cortex a focus of representation from which a muscle can be activated as an isolated or solitary response, or can be activated more strongly and more promptly than from adjacent regions. Only one such focus is found for each muscle and the focus of representation of two muscles in no case falls at exactly the same focus, even for two closely allied muscles such as tibialis anticus and abductor hallucis longus. . . . The evidence that this localization is a property of the Betz cells is suggestive if not conclusive." The authors later qualify this by saying that a cortical representation of muscles does not necessarily imply the existence of a mosaic pattern of strictly isolated subareas of the motor cortex, each dedicated to a single muscle.

Conflicting views are expressed by Mürphy and Gellhörn (1945). Their experiments on rabbits, cats and monkeys led them to the conclusion that stimulation shows great overlapping in the motor

cortex, the boundaries for movements of various joints of the arm or leg being practically co-extensive. Similarly one limb overlaps another. Overlap tends to decrease with encephalization, but is still considerable in the monkey. They observed that this multiplicity of representation persisted after isolation of a cortical spot so that it could not depend on physiological or physical spread. In their view variations of threshold depend on concentrations of ganglion cells in the fifth cortical layer. Bosma and Gellhorn (1947) obtained similar results. They maintain that stimulation of a cortical focus results in definite patterns of movement. Cortical foci consist of bands in which neurones innervating one muscle are intermingled with those innervating another. Stimulation may lead to co-contraction of antagonists. They say that "the demonstrated fact that movements induced by electrical stimulation of the cortex are co-ordinated in time and space suggests that the electrical stimulus elicits a process in the cortex through which the locally represented neurones are activated in certain patterns. The anatomical basis of muscular co-ordination is believed to lie, to a large extent, in the intracortical connections existing between neurones which, although supplying different muscles, are located in the same cortical focus. Were this not the case the various muscles would be activated in a strength commensurate with the number of neurones present, but without the temporal sequence which is characteristic of movements induced by cortical stimulation as well as by volition." Gellhorn and Johnson (1950) have stressed the importance of proprioceptor impulses in influencing the motor responses to cortical stimulation. They found that alterations in the posture of a limb modified its responses to cortical stimulation and they were agreed that neglect of this factor might help to explain the marked individual variability shown in the maps of the motor cortex in higher animals and in man. Hyde and Gellhorn (1951) have studied the effects of altering the frequency of cortical stimulation. They found that changing the frequency of stimulation might produce a shift from a flexor response to an extensor one and vice versa, and the two or more muscles activated from one cortical focus might have different frequency optima. Moreover the stimulus frequency optimal for a particular muscle at one cortical site might not be, and indeed often was not, the optimal frequency for the same muscle at a different cortical site.

Liddell and Phillips (1950) have also studied the effects of varying the frequency of stimulation. They have shown that the

areas of representation of various movements in the motor cortex of the baboon can be made to vary in size according to the parameters of stimulation and the level of narcosis. Using a single pulse stimulus they found that the movements elicited were confined to distal segments of the limbs and the face. The lowest threshold region was located in the middle third of the precentral gyrus which, with single pulses, yielded flick-like movements of the opposite thumb, index and little fingers, but no movements from other parts of the cortex nor of other parts of the body. With stronger pulses the thumb-index-minimus field expanded medialward and the medial part of the motor gyrus then responded, giving flick movements of the opposite hallux, either alone or with one or more of the other toes. At about the same strength, or a little more, the lateral part of the precentral gyrus yielded flicks of the tongue, or opposite angle of the mouth, or of both together. The threshold was always lowest for the "thumb complex", usually higher for the "toe complex", and highest for the "face complex". With stronger shocks and light narcosis, the three areas overlapped so widely that each shock caused flick-movements simultaneously in all three peripheries from the greater part of the motor area.

On the other hand when the frequency of stimulation of 50 c.p.s. instead of single stimuli was applied at the same strength the simple large-scale map of distal parts changed dramatically into the classical map of finer grain in which movements of all parts of the body were represented. These varying responses to variations in the frequency of the stimulus indicate the importance of the cortical threshold of stimulation in governing the motor response. Denny-Brown and Botterell (1948) state that a bilateral synergic movement of contralateral protraction (extension) of elbow and shoulder and flexion of hip and knee, with ipsilateral flexion of elbow and shoulder and extension of hip and knee, is obtainable from the forward medial zone of area 4 by bipolar electrical stimulation.

We shall now leave the consideration of electrical stimulation of the cortex in order to consider the effects of ablation, though stimulation will again have to be mentioned in connection with the effects of the removal of different areas.

The Effect of Cortical Ablations upon Movement

Fulton and his collaborators in a series of papers have drawn a distinction, based mainly upon ablation experiments in the

chimpanzee, between the functions of the motor and premotor areas. Fulton uses the term motor area as corresponding to the distribution of the Betz cells, i.e., area 4 of Brodmann. He uses the term premotor area to describe the cyto-architectonic field designated area 6a (upper part) as outlined by the Vogts and Foerster. His views on the differences in the functions of these two areas are summarized in his book (1949).

According to Fulton, complete experimental ablation of area 4, the motor area, causes transient paralysis, most marked and enduring in the distal joints, transient depression of reflexes and transient flaccidity. In the stages of recovery from a lesion of area 4, deep reflexes may become moderately hyperactive, but gross spasticity has never been observed at any stage of recovery following lesions sharply restricted to area 4. Ablation of area 6a (upper part), premotor area, at a primary operation, or after removal of area 4, causes a disorganization of the more integrated voluntary movements producing a state which, following a suggestion of Walshe (1935), Fulton recognizes as akin to apraxia in man. Lesions of this area also lead to immediate appearance of spasticity with increase in deep reflexes, forced grasping, vasomotor disturbances and certain specific reflex signs, such as those of Rossolimo, Mendel-Bechterew, Hoffmann and the fanning sign of Babinski. Bilateral ablations of the motor and premotor areas in mature monkeys cause permanent paralysis of the voluntary movements, and the postural reflex state of the skeletal musculature of such a preparation is indistinguishable from that of a thalamic monkey. Fulton therefore regards spasticity, the appearance of certain reflexes, forced grasping and the disorganization of the more highly integrated movements as the outcome of damage to the premotor area, which, he holds, utilizes an extra-pyramidal pathway.

Denny-Brown and Botterell (1948) have reported the results of an elaborate series of ablation experiments in the macaque monkey. These authors were impressed by the fact that the disorder of movement resulting from cortical ablation was not only transient, but also relative and not absolute. They found that no single type of gross behaviour, such as progression, standing, grasping objects, emotional display, or feeding was exclusively affected by any of the varied types of lesion made in areas 4 or 6 of the cortex. On the contrary, any weakness or paralysis that was produced was always most apparent in simple isolated purposive movements when the animal was tired, was less apparent

when the movement was motivated by desire to escape from his captor, was still less severe when the animal clutched at objects in falling, and was often not appreciable at all when the limb was used in behaviour motivated by strong emotion. They state that "none will deny that portions of some single muscles can be contracted by stimulation of the cerebral cortex, and in that sense are 'represented' in area 4", but the physiology of reflex function indicates that the cortical mechanism probably does not use muscles individually, any more than a spinal reflex is made up of either a whole single muscle or all the movements represented in a spinal motor nerve root. The result of ablation of the Betz-cell cortex was a depression of motor function affecting all motor activities of the opposite side. Various types of motor function were affected in different degrees, and movements in the hand and foot were more severely affected, and for a longer time, than movements involving proximal joints. Their observations suggested to them that movements were not lost, but that their mechanism was depressed by area 4 lesions and they were revived, not by vicarious function from some new centre, but by a circumstance which counteracted the process of depression.

The Functions of the Motor Cortex

We must now see whether it is possible to explain the conflict of views about the functions of the motor cortex, which have been described above, and how far they can be reconciled with each other. Walshe, in a series of papers, has criticized what may be called the punctate localization theory and contrasted with it the conclusions which can be drawn regarding the cortical organization of movement from clinical observation to which Hughlings Jackson contributed so greatly. In a critical review on the subject of the giant cells of Betz, the motor cortex and the pyramidal tract, Walshe (1942) first considers what is meant by the term Betz cells.

His study is limited to two areas: (1) the area immediately anterior to the fissure of Rolando (Brodmann's area 4) and (2) the area lying anterior to the preceding (Brodmann's area 6). These two areas make up the agranular frontal cortex, so-called because the two granular layers II and IV of the cortex are virtually absent. From the second to the fifth layers inclusive, the nerve cells are all of pyramidal type, though histological classification has in the past recognized three categories of large pyramidal cells, Betz cells, simple giant cells and large pyramidal cells. Walshe

believes that every possible transitional form between the members of this conventional grouping is to be seen, both in the adult and in the infant cortex. Hence "the Betz cell is no more than the largest and the most massive member of the large group of pyramidal cells". The pyramidal cells reach their final development in layers V and III, the Betz cells being virtually confined to layer V.

The posterior boundary of the Betz cell area lies almost at the bottom of the fissure of Rolando. The limits of these cells on the mesial aspect of the hemisphere in the paracentral lobule are also fairly clear, but the anterior border of the Betz-cell-bearing area cannot be sharply delimited, because, as the cells are traced forwards, they diminish progressively in size and their differentiation from simple giant cells and from some large pyramidal cells becomes increasingly difficult. When the distribution of the simple giant cells and of the large pyramidal cells is considered, it is found that the superior and posterior limits of this coincide with those of the Betz cell area, but that the anterior and the lower limits extend over a larger area. Walshe suggests that in relation to physiological function the important factor may be, not the structure of the cortex over the whole, but the structural uniformity of a single cortical lamina. For example, there are reasons for believing that the motor cortex and its projection into the pyramidal tract, are largely, if not wholly, based upon the fifth cortical lamina which possesses a structural uniformity over an area as wide as that of cortical area 4 and the adjacent posterior part of area 6.

Turning now to physiological experiments designed to determine the extent of the motor cortex and its functions, Walshe expresses the view that, despite recent claims to the contrary, physiological experiment does not confirm that the motor cortex can be divided into two separable components of distinct and different functions. On the other hand, experiments show that the motor cortex is one and indivisible. It embraces the whole of area 4 and the adjacent posterior part of area 6. It appears that the motor cortex is not co-extensive with a cortical "area" but that the true correlation of function and structure is between motor function and the large pyramidal cells of layer V in areas 4 and 6.

Walshe next considers the cortical cells of origin of the pyramidal tracts. There is reason to think that the Betz cells alone are insufficient for this purpose, and both the anatomical and physiological evidence points to the conclusion that in layer V (possibly

also in layer III C) of the cortex there is a group of large pyramidal cells which include the giant cells of Betz, the simple giant cells and the large ordinary pyramidal cells, and that the axons of this group subserve the function of a projection system for the motor cortex. The cortical region in which these cells are found and from which therefore this pyramidal system arises includes the whole of area 4 and the posterior, adjacent part of area 6.

Walshe (1943) next turns to the consideration of the mode of representation of movements of the motor cortex with special reference to "convulsions beginning unilaterally" in Hughlings Jackson's phrase. He points out that in Hughlings Jackson's view the "hand area", for example, is not merely the cortical region in which movements of the hand alone are represented, but one in which the movements represented are mainly and predominantly those of the hand. Conversely, this area is not the sole region of representation of hand movements, for these are represented subordinately throughout the motor cortex, the so-called "hand area" being as it were simply a focus of their representation. "Thus the motor cortex is to be conceived, not as a mosaic of abrupt localizations, but as a complex pattern of overlapping and graded representations." Clinical observation therefore suggests that movements are organized in the motor cortex in the form of wide overlapping fields in what Jackson calls the "leading part", that is, the thumb and index finger, the lower part of the face and the foot, are particularly wide areas of representation. Jacksonian convulsions, Walshe suggests, almost always begin in one or other of these leading parts because the movements concerned are those that have the widest field of low threshold excitability, a suggestion recently confirmed by the experimental observation of Liddell and Phillips (1950) described above. Similarly the high degree of recovery of function after local ablation of the motor cortex in anthropoid apes and monkeys is to be explained by the fact that movements are also represented in areas of the motor-cortex other than that excised. Such observations are incompatible with the view that individual muscles are represented in the motor cortex, as is also the fact that in hemiplegia in man a muscle may participate in one movement although it cannot be brought into action in another.

How, then, are the observations of those physiologists who claim to have been able to elicit contraction of a single muscle, or even part of a muscle, by localized stimulation of the motor cortex to be explained, and what is their significance? Walshe

points out that "electrical stimulation" appears to "sample" the motor cortex, revealing "fragmentary reactions", but not clearly revealing the general design of the cortical representation of movement. The method by which these items of movement are evoked is so remote from anything normally obtaining that we cannot even be sure that what we see are in truth normal components—physiological units—of cortical function. Walshe (1951) stresses the importance of taking an operational view of the interpretation of experimental studies of cortical motor function. We ought not, he says, to "regard the items of movement evoked by stimulation, or the cortical diagrams from which we symbolically represent them, as being any more than simple observations and their records. They are not expressive of theories of functions." Similarly, Denny-Brown (1951) remarked that writers on the frontal lobe "showed charts of symptoms or of electrical effects as if these were in some way equivalent to function. The only key to the problem of function in the central nervous system is the Sherringtonian definition of the adequacy of stimulus." Hence, for example, the statement that cortical stimulation can evoke contraction of a single muscle merely means exactly what it says with the, often unspoken, addition that this occurred with a certain strength of frequency of stimulus, the animal being under certain depth of anaesthesia with a given pre-existing posture of the limbs, and so on. A result which may depend, for example, upon the threshold of response of anterior horn cells of the spinal cord to excitation of pyramidal fibres should not be taken to mean that a muscle is "represented" as such in the motor cortex in the sense that in normal voluntary movement the motor cortex operates by, as it were, selecting the individual muscles suitable for the purpose. As Walshe (1943) puts it, "if the cortex represents only elementary units of movement, then a normal purposive movement-complex results from a 'making up' of units. If, on the other hand, we suppose such movement-complexes to be laid down as such in the cortex, then the item of movement evoked by a brief electrical stimulus results from a 'breaking up' of this representation."

The stress laid by Denny-Brown upon "adequate stimulus" is a salutary reminder that even the concept of voluntary or willed movement may easily be an artificial abstraction. He points out the importance of visual and tactile stimuli for the normal functioning of area 4. Gooddy (1949) reminds us that "in voluntary movements, sensation and motion form a single

indivisible continuous process". Hughlings Jackson (*Selected Writings*, vol. 1, page 414) speaking of the two highest levels of the nervous system, i.e. the "motor cortex" and the "organ of mind" said:—"These levels are, as the lowest level is, sensorimotor, but I find it possible to illustrate by motor centres only, not, however, believing that these so-called 'motor centres' are purely motor."

Spasticity

Fulton's views as to the relationship between lesions of area 4 and area 6 and the development of spasticity in the contra-lateral limb have been described above. This question has recently been reinvestigated by Denny-Brown and Botterell (1948). They found that spasticity accompanied the paralytic manifestations of all area 4 lesions, and was most prolonged in total lesions. Its rapidity of development depended on the extent of depression of motor function concurrently produced. Ablation of area 6 as well as area 4—either in one operation or in two stages—led to a greater spasticity in the flexors of elbow and extensors of knee and ankle than occurred after area 4 lesion alone. The intensity of resistance was not greatly increased, but the clasp-knife phenomenon was more commonly obtained and the hemiplegic posture more obvious. Ablation of area 6 alone led to the appearance of a slightly flexed posture in both the upper and lower contralateral limb. There was a soft plastic type of resistance in both flexors and extensors of the knee and hip, elbow and shoulder, without change in the tendon reflexes. The authors point out that spasticity, like movement, has to recover from the spinal shock or reflex depression that follows any corticospinal lesion and that this shock is the greater the larger the extent of area 4 excised. The survival of even a few Betz cells in an area of ablation lessens the spinal shock and in so doing alters the outcome.

Hines (1937) observed a zone lying in the premotor area between area 4 and area 6 removal of which caused contralateral spasticity, while its stimulation caused a relaxation of muscle tone of the opposite side. Magoun and Rhines (1947) describe a projection from area 4s of the cortex to the bulbar reticular formation to which is attributed a powerful inhibitory influence upon muscle tone. They regard spasticity as an exaggeration of spinal stretch reflexes which results from the impairment of central inhibitory influences which normally reduce them. Spasticity depends at the same time upon the activity of a reticular spinal facilitatory system.

Suppressor Zones

The observation that relaxation of muscle tone can be obtained by stimulation of the cortex is an old one. Recent studies have suggested that a suppressor influence is exerted by particular anatomical zones of the cortex. A critical review of this question, accompanied by fresh observations on the cat, was published by Druckman (1952). He gives the history of the idea, but states that he was unable to confirm the existence of suppressor areas in the cat. He points out that the concept of suppression includes three separate phenomena, namely, spreading depression, inhibition of muscle tone and inhibition of cortically-induced motor after-discharge. Each of these effects have been obtained from regions other than those designated as suppressors. Since these phenomena are unrelated he suggests that the term suppression should be discarded and the appropriate physiological term used instead. Two cortical areas need special mention in this connection. The effects of stimulation and ablation of area 4s, observed by Hines, have been described above. Druckman points out that area 4s is the only one of the so-called suppressor areas found to connect with the reticular formation. Particularly powerful suppressor activities have been attributed to the anterior cingulate region areas 24s. This has been confirmed by Druckman who points out that stimulation of this area produces inhibition of cortically-induced movements. This inhibition is not associated with contraction of the antagonists of the muscle in question, which shows that inhibition, as distinct from reciprocal inhibition, can be elicited from the cerebral cortex.

The Grasp Reactions and the Organization of Movement

Hughlings Jackson's prescience has found confirmation in the observation of Denny-Brown and his colleagues on the grasp reactions and their significance for the organization of movement. Denny-Brown (1951) has recently reviewed this question. He first distinguishes from the true grasp reactions a form of reflex flexion which occurs after removal of area 4 in the monkey. This occurs when traction of the forearm induces flexion of the wrist, elbow, and shoulder, and if the fingers are pulled on, the digits flex strongly also. This response to traction occurs first only under emotional stress, but is soon put to some purpose by the animal.

This response is primarily proprioceptive and is not abolished by denervation of the hand and it can be produced by traction on the shoulder alone. Denny-Brown states that this response is also present in the recovering phase of cortical hemiplegia in man. Denny-Brown and Twitchell (1950) have found it present after section of the medullary pyramid in the monkey and on hemisection of the spinal cord.

Denny-Brown states that an important series of reactions remain completely absent after ablation of area 4 in the monkey. If the eyes of a normal animal are blindfolded and he is brought to the edge of a table so that some part of the hand or foot touches the edge, the limb is normally raised and the hand or foot gently placed on the upper surface. This is the tactile placing reaction. If performed by a visual stimulus, the reaction is the visual placing reaction. If some displacement of the limb is required in the absence of vision it is a proprioceptive placing reaction. It has been shown that after ablation of either the sensory cortex or area 4, the tactile and proprioceptive reactions are absent, though in time some slight proprioceptive reactions return. The parietal sensory cortex is essential to a tactile placing reaction in the opposite limb, initiated in the limb. After removal of the post-central cortex on one side, tactile placing in the opposite limb can be initiated by contact from the ipsilateral side (crossed tactile placing), but not from contact with the limb itself.

An investigation of the grasping automatisms in man by Seyffarth and Denny-Brown (1948) led them to differentiate these reactions into the grasp reflex and the instinctive grasp reaction. Denny-Brown believes that much of the confusion regarding the meaning of forced grasping arises from the failure to differentiate the proprioceptive righting reaction just described from the true grasp reflex. According to him the latter in its two forms, contactual reflex grasping and instinctive grasping reaction, does not follow ablation of either area 4 or area 6, but is seen after removal of areas 8s and 24s which are both suppressor bands. The grasp reflex, the tactile placing reaction, and the instinctive grasp reaction are all aspects of the same mechanism, an adjustment of the animal to spatial contact.

Denny-Brown concludes that the adequate stimulus for the motor reactions of area 4 is contact, both light and heavy contact, and that the whole sensori-motor cortex of areas 4, 3, 1 and 2 work as a unit in this regard.

The Supplementary Motor Area

A supplementary motor area of the cortex has been described by Penfield and Welch (1951) and their account is summarized, together with fresh observations, by Penfield and Jasper (1954). The observations of Penfield and Welch were made both on human beings and on monkeys. They revealed that in a relatively small zone of each hemisphere, anterior to the motor area for the lower extremity, there exists an area which yields characteristic responses to stimulation. This, the supplementary motor area, is situated almost altogether within the median longitudinal fissure and anterior to the primary motor area for the foot. They found that the threshold for stimulation of the supplementary motor area was a little higher than for the precentral and postcentral regions. In the monkey stimulation of the supplementary motor area revealed a motor representation of the contralateral extremities with a definite topographical organization which it had not been possible to reproduce in man. In view of the previously observed associations between removal of this area of the cerebral cortex and the appearance of reflex grasping in the monkey, it is interesting that Penfield and Welch found that they could produce inhibition of spontaneous grasping in the opposite hand by stimulation of the supplementary motor area and removal of that area resulted in forced (or "reflex") grasping.

Penfield and Jasper classify the effects of stimulation of the supplementary motor area under the following headings: vocalization, general movement, arrest or slowing of voluntary action, autonomic change, sensation, aphasia.

Vocalization has been produced repeatedly. Among general movements leg movement as an isolated phenomenon occurred only twice, but arm movements were produced nineteen times in eight patients. These were most frequently seen at the elbow and shoulder and rarely involved the fingers in contrast to responses of the upper extremity from stimulation of the precentral gyrus. Movement produced by stimulation of the supplementary motor area consisted of (1) the assumption of a posture; (2) repeated or continuing manœuvres or rhythmic movements and (3) rapid inco-ordinate movements which occurred much less frequently. Arrest or slowing of voluntary action was a frequent result of stimulation of this area and was observed after stimulation at forty different points in eighteen patients. This inhibition applies most often to speech. Autonomic changes consisted most

frequently of pupillary dilatation, but acceleration of heart rate was also observed. Sensations which have often been difficult to describe have occasionally been elicited. Aphasia is a defect in speaking which is different from the arrest of speaking referred to above.

Supplementary Motor Seizures. Penfield and Jasper apply this term to epileptic attacks originating in, or involving, the supplementary motor area and they quote examples. It appears that the most characteristic feature of such attacks is the development of a posture, for example, turning of the head and eyes to the opposite side with involuntary raising of the opposite upper limb. There may be sensory accompaniments and spread of the epileptic discharge from the supplementary area back into the primary motor area may produce clonic movements.

The Effects of Hemispherectomy

The effects of the surgical removal of one cerebral hemisphere in man extend far beyond its physiological implications, and these beyond the light which it throws upon the organization of movement. Nevertheless since its therapeutic value has still to be assessed, and its physiological interest in relation to the organization of movements is considerable, it is perhaps most conveniently considered at this point.

Krynauw (1950) reported the result of twelve hemispherectomies carried out over a period of five years on patients suffering from infantile hemiplegia. He regarded convulsions and mental changes as the indications for operation. Epilepsy, either focal or generalized, was present in ten out of his twelve cases and in all these the epileptic manifestations ceased after operation without sedative medication. Disorders of behaviour and personality were a marked feature and a profound betterment in respect of mentality was observed in all cases. Krynauw points out that this improvement in the mental sphere presupposes and is dependent upon the integrity of the remaining cerebral hemisphere and its ability to function normally once it has been released from abnormal influences from the pathological side. In this connection it is interesting that the removal of the affected hemisphere caused an improvement in the electro-encephalographic abnormality in the normal hemisphere which leads Krynauw to conclude that the dysrhythmia encountered in the normal hemisphere was due in the first instance to an overflow from the grossly abnormal high amplitude components of the opposite and

pathological hemisphere via the interhemisphere communicating pathways.

The survival of motor and sensory functions on the contralateral side after hemispherectomy are a surprising feature. Krynauw notes that if the caudate nucleus is removed with the hemisphere there is little or no return of voluntary and useful motor activity, and he infers that the persistence of motor functions, together with improvement in muscle tone after the operation, depends upon the activity of the remaining cerebral hemisphere which, he holds, is exerted via the caudate nucleus of the contralateral side.

On the sensory side he found that localization of pin prick returned after a few months with only a minimal defect of accuracy. Joint sense also returned with the lapse of time in at least two cases, accurately in the largest joints and in one case at the wrist and even in one case for gross movements of the fingers. Two-point discrimination with an increased threshold—about three times the normal—was present in two of the cases he examined.

Bates (1953) has made some observations on the excitability of the human cerebral cortex after the operation of hemispherectomy. In a consecutive group of ten patients undergoing this operation for infantile hemiplegia a portion of the *falx cerebri* was excised after removal of the diseased hemisphere. In this way the medial surface of the sound hemisphere was exposed for stimulation. It was found that half the excitable points on the medial surface gave movements commencing in the contralateral leg; the remainder gave movements commencing with the ipsilateral (hemiplegic) leg, the contralateral arm and the ipsilateral arm in that order. Bilateral leg movements were sometimes seen, but in two cases movement of three limbs was produced and in one case movement of all four limbs from stimulation of a single cortical point. These complex responses could readily be obtained on repetition and they did not resemble responses obtained from the motor region of the lateral surface of the brain under similar conditions, and were in no way similar to movements seen accompanying epileptic discharges. They resembled in some respects the assumption of a posture, or the performance of components of a simple act such as climbing.

Bates discusses the significance of his observations in relation to those of Penfield and Welch on the supplementary motor area and also the current conception of a primary motor area for the lower limb at the vertex and of the medial aspect of the

hemisphere. Bates points out that the evidence for such a primary motor area for the unilateral representation of the lower limb is rather scanty and suggests that there may be a relatively strong bilateral representation in the primary leg area in each hemisphere in man. Nevertheless, he admits that the repeated appearance of complex patterns of movement of the arms and legs from stimulating one point is quite unlike anything seen from the convexity under similar conditions. To that extent, therefore, Penfield's claim for a supplementary motor area must be supported, together with his observation that such points are anterior to the region where one would expect the primary leg area to be. In movement which involves the toes, the great toe and the remaining toes more often than not responded in different ways. In two of the patients a withdrawal of the lower limb with upgoing great toe was produced on the hemiplegic side from cortical stimulation.

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CHAPTER 2

THE FRONTAL LOBE—MENTAL ASPECTS

As already described, that part of the frontal lobe which lies anterior to areas 4, 6 and 8, that is, the motor and premotor areas and the frontal eye field, is known as the prefrontal area or the frontal association areas. Experimental stimulation of this area in animals does not evoke movement, and in primates, according to Fulton, no reflex changes in the skeletal muscles and no obvious alterations of posture follow extirpations sharply restricted to the prefrontal areas. Bilateral removal of the prefrontal areas in monkeys, however, produces conspicuous changes in behaviour. After unilateral removal no disturbance of behaviour, or of the higher intellectual functions, can be detected; but, after bilateral removal, many observers have reported a striking restlessness, distractibility and a ravenous appetite. The studies of Jacobsen and his colleagues of the effects of bilateral removal of the frontal areas in chimpanzees has been illuminating. When tested by means of problems which involved the retention and utilization of recent sensory experience, the operated animal failed, and when, for example, food was placed under one of two cups and a screen was lowered between the animal and the test object, the animal was unable to remember under which cup the food was hidden even after four or five seconds, whereas a normal chimpanzee would find the correct cup after delays as great as five minutes. Jacobsen, moreover, found that an animal, which, like Pavlov's dog, developed neurotic symptoms when its discriminative powers were subjected to too great a strain, remained completely placid when put to the same test after removal of both frontal areas.

Messimy (1939) draws attention to the most intense motor activity which follows bilateral excision of the prefrontal regions in apes. The operated animals appeared to react more violently to external stimuli than before the operation, and their instinctive reactions were exaggerated and showed lack of inhibition. Messimy also noticed a number of autonomic disturbances including excessive appetite, exaggerated reactions to drugs, such as adrenaline, variability in cardiac rhythm and irregular emptying of the

alimentary tract. There was a generalized hyperplasia of the animal's lymphoid tissue, and the thymus increased in size, which Messimy interpreted as a sign of rejuvenation.

During recent years unilateral frontal lobectomy in man has been carried out on numerous occasions; and the effects of the bilateral operation have also been studied. As to the effects of the unilateral operation there is some difference of opinion. Penfield and Evans (1935) found that the maximum amputation of the right or left frontal lobe alone produced little change in the mental life except for some impairment of those processes necessary for planned initiative. Jefferson (1937) concluded from eight cases of unilateral frontal lobectomy that "it appears to be quantity, volume, that matters most, even in man and not alone in the lower animals as Lashley's work has suggested. No one will deny that the frontal lobes are deeply concerned in intellectual processes and emotional control, but they are not the only parts of the cerebral mass involved in these activities. It is clear that in a single frontal lobe mental processes have no closely packed, essential or solitary locus the withdrawal of which leads to a state of dementia, partial or complete, and that the brain must function intellectually and emotionally as a whole, in the sense of Hughlings Jackson, rather than in the departmental way that anatomical research once suggested".

Brickner (1936, 1939) has made a remarkable study extending over some eight years of a forty-year-old stockbroker who had a bilateral frontal lobectomy carried as far back as the premotor region. The patient's intelligence quotient varied between 80 and 99, depending upon his co-operation and ability to concentrate. He was strikingly euphoric, and his behaviour was puerile. *Witzelsucht* was conspicuous and there were constant clowning and punning. The patient showed a gross lack of appreciation of his own condition and loss of initiative. He still expressed an ardent wish to return to work as a stockbroker, but made no move to carry it out. He was readily distracted, selfish, tactless and inconsiderate, and often rude. Sexual tendencies were uninhibited, and masturbation occurred. In his second report Brickner (1939) states that the patient has learned nothing since his operation beyond the simplest things which happen around him. From the standpoint of intellect, time has stood still for him. Brickner considers that the fundamental defect resides in the patient's powers of mental synthesis, that is, in the assembling of groups of percepts into groups of a higher order.

Rylander (1939) has published a valuable study of personality changes after operations on the frontal lobes. He reviews the literature and reports 32 cases which have been under his own observation and subjected to psychological tests.

Rylander draws attention to the importance of the patient's preoperative personality in interpreting his condition after operation and also the difficulty of explaining the mode of origin of certain symptoms, for which different psychological theories might account in different ways.

Emotional changes occurred in 30 cases. These consisted of a diminished inhibition of affective responses in 25 cases and a displacement of the habitual feeling-level in 28 cases, in 20 towards euphoria and in eight towards depression.

Changes in volitional and psychomotor activity occurred in 22 cases. Fourteen patients showed restlessness and 12 deterioration of initiative and interest. These symptoms sometimes appeared together. Intellectual changes, mainly involving the higher faculties, occurred in 21 cases. The more automatic forms of intelligence remained relatively well-preserved. Attention, memory and the ability to grasp the more common situations were not disturbed to any considerable extent, but the more complicated intellectual processes, which included higher forms of reasoning, thinking in symbols, and judgment had deteriorated. Rylander concludes that the procedure adopted does not permit definite conclusions on the nature of the normal functions, damage to which gives rise to the pathological features described, nor is the conclusion permissible that these functions are localized in the frontal brain just because they suffer in cases of frontal lobe lesions.

Freeman and Watts (1939-9) draw certain conclusions as to the functions of the frontal lobe from their observations made in 48 cases of prefrontal lobotomy (leucotomy). This surgical procedure and the light it throws on frontal lobe functions are considered below.

If further evidence were required for the powerful nexus between psychiatry and neurology and justification for the term neuropsychiatry, it would be provided by the surgical procedure known as prefrontal leucotomy. We would not go so far as to sanction the use of the barbarous term "psycho-surgery", employed by two of the leading exponents of the operation; but the fact remains that we are now in a position to cure or ameliorate biogenetic psychoses and psycho-neurotic reaction-formations by means of cerebral surgery.

Prefrontal Leucotomy

Historical. Trephining was resorted to in prehistoric days, presumably to provide an exit-hole for the evil spirit responsible for mental disorder. For countless centuries attempts were made to dislodge the evil spirit by various forms of magic and incantations, or by making its inhabitant so uncomfortable by ill-treating the host in various ways (ducking, beating, chaining, mocking, etc.) that it would gladly take its departure. It is always wise to remember the humble origins of our most modern "scientific" procedures. It was not, however, considerations of that kind that led Moniz to perform the operation of prefrontal leucotomy on psychotic patients. He had (presumably) noted the experimental work on primates by neuro-physiologists such as Victor Horsley, Fulton and Jacobsen. It was, for instance, a striking fact that, after resection of the frontal lobes, chimpanzees became gay and irresponsible. Memory of recent events became grossly impaired; and there was marked distractibility of the kind associated with mania in the human being. As Pavlov was well able to demonstrate, animals as well as humans can become neurotic. One "temperamental", neurotic chimpanzee used to fly into temper-tantrums whenever she could not accomplish a set task to her own satisfaction. After bilateral resection of the frontal lobes, she became insouciant and showed no emotional upset when her performances were frustrated. Similar absence of worry and foreboding had been clinically noted in the case of persons who had suffered bilateral injury in the prefrontal areas. Moniz, then, was well provided with experimental and clinical data before he decided to experiment on human beings in 1935; but he must have required an immense amount of courage. He published an account of his first results in 1936. A year or so later, in the U.S.A., Lysterly, Freeman and Watts, Love and others took up the work, and modified the surgical procedure.

In Great Britain, active interest in prefrontal leucotomy was not aroused until the early 1940's. The leading surgical exponents include McKissock, Knight and Harvey Jackson. Some 10,000 leucotomies have been performed in Great Britain up to date.

Technique. In the words of Knight, "prefrontal leucotomy consists essentially in the division of the central core of white matter within the frontal lobes with a minimum disturbance of the cortex and the subcortical tissues." This is not the place to give a detailed description of the operation or the apparatus used,

if only for the reason that each surgeon seems to have evolved his own technique and apparatus. With regard to apparatus, some surgeons (including Moniz himself) used a special apparatus called the leucotome which is like an elaborate apple corer, but which leaves the core which it cuts *in situ*; others prefer to operate with a nasal elevator; one surgeon finds a paper knife an ideal instrument. Some surgeons are confident about performing the operation "blindly" through burr-holes made in the coronal suture, relying on superficial landmarks and measurements to guide them; others prefer to rely on direct vision by enlarging their trephine-holes and using a brain-speculum. The operation in all its stages can be carried out under a local anæsthetic; the average institutional patient selected for operation is likely to be too emotionally-disturbed for this to be an agreeable experience for the surgeon. The trephine-holes are made at a point 3 cm. behind the outer angle of the eye and 6 cm. vertically above the zygoma. This point, on most skulls, will be found to be just in front of the junction of the coronal and temporal sutures. The division of the white matter is made in the plane of the coronal suture. It would appear to be unsafe to introduce the cutting instrument to a greater depth than 4.5 cm. in the medial direction, but metal callipers applied to the trephine-holes should be used to measure the width of the brain, from which measurement the amount of white matter in each frontal lobe can be estimated. The exact plane of the cortical incision is of the greatest importance. If it is too anterior, the effects of operation will be small; if it is made too far posteriorly, the effects will be profound, amounting in extreme cases to the organic-reaction type of psychosis and dementia. Care must be taken to avoid puncturing the ventricle or damaging cerebral vessels. Most of the deaths attributable directly to the operation have been caused by intracerebral hæmorrhage from damaged vessels. An experienced surgeon by taking simple precautions, is usually able to avoid these two accidents. Moniz at first destroyed the white matter by means of alcohol injections; but, finding this method unreliable, he soon gave it up in favour of the cutting method.

Technique (Variations). The technique just described has come to be known as the *standard* operation; but many variations have been devised all of which have their supporters. Most of these departures from the standard technique aim at limiting the destruction of tissue to the lower and medial quadrants, as it was found that the more posterior was the damage to the

thalamo-frontal radiations the greater were the undesirable and irreversible changes in the personality-structure to be expected.

Scoville, for example, advocates an operation, which has come to be known as "Undercutting", which involves the orbital surface of the frontal lobes only.

The late Sir Hugh Cairns was in favour of a similar open operation involving the cingulate gyrus of the frontal lobes.

Spiegel and Wycis in the U.S.A. are the exponents of an operation which by a thermo-electrical technique coagulates certain nuclei of the thalamus itself. They claim to be able to reach their target with extreme accuracy by means of their special "stereotaxic" method.

Freeman is the chief exponent of Fiamberti's trans-orbital approach, and claims results which compare favourably, both from the point of view of symptomatic improvement and safety, with more elaborate surgical procedures. This method which produces a deep frontal cut in the lower medial quadrant has the great advantage of being able to be performed by a surgically-minded psychiatrist himself when the services of a neuro-surgeon are not available. However, on many counts, this is not an operation that commends itself to us.

McKissock performs a closed operation from the sides in cases of schizophrenia and operates from above and more "rostrally" in the neuroses.

Many of these approaches are shown in Fig. 1.

Early Effects of Operation. The immediate effects of operation are frequently quite dramatic. As soon almost as the fibres have been divided on both sides, the patient loses his nervous tension, and the face takes on a mask-like expression. Many patients who have had the operation under a local anæsthetic describe this instantaneous relief as the most wonderful experience. There are a great number of immediate post-operative effects, lasting in some cases a matter of two or three days and in others for several weeks. For the first four or five days, a slight rise of temperature is to be expected with mild headaches, somnolence and occasional vomiting. Amnesia is an almost constant temporary symptom. Among the more important neurological temporary signs and symptoms produced by prefrontal leucotomy we may mention plateau speech, vomiting, akinesia, urinary and faecal incontinence, sweating, blood-pressure changes, convulsions, extensor plantar responses, borborygmus, localized paresis, aphasia, hemiplegia, ataxia. In some cases, one or more of these

signs and symptoms take on a persistent character. The same remark applies to the temporary psychiatric symptoms, the most important of which are apathy followed by over-activity, dullness, disorientation, euphoria, fatiguability, impaired attention, retardation, laziness and indifference, somnolence, playfulness and facetiousness, perseveration, mannerisms, stupor, indecency.

Late Results of Operation and Modus Operandi. According to Freeman and Watts, the prefrontal regions in man are concerned with foresight, imagination, and the apperception of the self. These psychological functions are invested with emotion by way of the association fibres that link the prefrontal regions with the thalamus and the hypothalamus. It would seem, then, that the functions of the prefrontal lobes are concerned with the adjustment of the personality as a whole to future contingencies. The imagination, therefore, in the pure sense of the term, may be said to reside in the prefrontal areas. Pure intellection in the sense of analysis, synthesis and selectivity do not appear to require the integrity of the frontal and prefrontal areas to the extent that was previously thought necessary. In this connection, it is instructive to note that, after prefrontal leucotomy, the only really significant changes shown by pure intelligence tests are a poorer performance in the "free association" Stanford-Binet tests, and reduced initiative in starting all the tests.

Therefore, as we should expect, the most striking feature of prefrontal-leucotomized patients is their lack of self-consciousness

FIG. 1. American Leucotomy Techniques (Scoville)

1. (a) Scoville's orbital undercutting.
 (b) Scoville's undercutting of superior convexity.
 (c) Grantham's electrocoagulation of inferior medial quadrant.
 (d) Spiegel and Wycis' stereotaxic electrocoagulation of thalamic nucleus.
2. (a) Scoville's cingulate gyrus undercutting. Livingston's cingulate gyrus subcortical sectioning.
 (b) Freeman and Watts' "closed" standard lobotomy.
 (c) Medical inferior quadrant section by McKenzie's leucotome method, Schwartz' nasal speculum method, Grantham's electrocautery method and Poppen's direct vision suction and spatula method.
3. (a) Poppen's "open" standard lobotomy under direct vision. Freeman's transorbital lobotomy.
 (b) Arrows indicate deep frontal cut.
 (c) Pool's topectomy operations.

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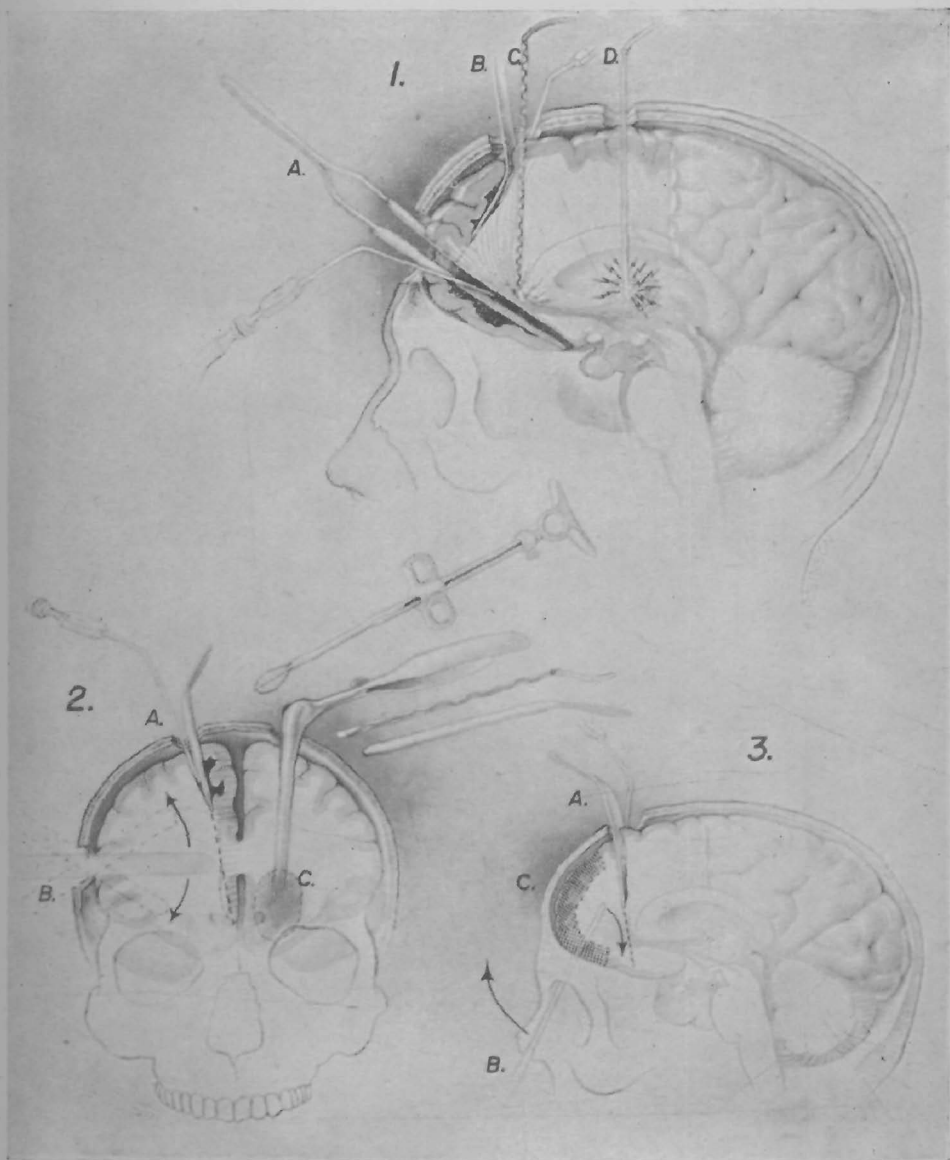


FIG. 1. (For explanation see opposite page).

and their ease and freedom in social relationships. This "*Distanzlosigkeit*" can sometimes be embarrassing to others, although not to the patient. The picture is frequently a combination of euphoria, distractibility and gay irresponsibility, almost amounting to hypomania. However, especially when a great amount of white matter has been cut, the picture is sometimes one of inertia and contented indolence rather than of hypomanic drive. Occasionally, a great deal of aggression is released by the operation. Freeman and Watts relate the history of such a patient, who, after operation, ruined his career, alienated his friends and family, and figured in a number of law-suits, some for physical violence, but who, for all that, went about "munching candy and declaring that he had never felt better in his life." The emotional tone with which functions mediated through the frontal lobes are endowed is probably provided by the thalamus or hypothalamus; or conversely, one might say with equal truth that frontal lobe centres have a supporting effect upon the activities of the emotional centres in the thalamus and hypothalamus. T. P. Rees translates this psycho-physiological concept into psycho-analytical terms and, rather fancifully, locates the *super-ego* in the prefrontal areas and the *id* in the thalamus. Therefore, in dividing the links between these two areas, the *id* is relieved from the tyrannical supervision of the over-active *super-ego*. He says that among the most common symptoms of mental conflict are anxiety, groundless fears about the future, suicidal tendencies, self-mutilation, states of tension, destructiveness and attacks of uncontrollable violence, and that it is patients who exhibit severe symptoms such as these who derive the greatest benefit from prefrontal leucotomy.

The following, then, are some of the many later symptoms produced by prefrontal leucotomy; lack of initiative, euphoria, procrastination; laziness, tactlessness, increased or decreased suggestibility, indefatigability and youthful appearance. Sometimes, as we have already stated, the change in the total personality is rather disconcerting, and might give some concern to the moral theologian. However, even if a patient is unable to return to a useful career in the outside world, to quote Freeman and Watts again, "a contented drone is better than a complaining one".

Partridge, by personal interviews with the patients concerned and their relatives, followed up 300 cases over a period ranging from one-and-a-half to three years. His results were published in 1950 in his book entitled "Pre-frontal Leucotomy". This book is

a model of its kind and should be carefully studied by any neuro-psychiatrists who are called upon to give advice when prefrontal leucotomy in any of its forms comes up for consideration.

Indications for Operation. Since functions not diseases are represented prefrontally, it is impossible to give the indications for prefrontal leucotomy in terms of nosology. The symptoms are obsessive preoccupation and agitation. These symptoms are frequently found in almost any kind of mental disorder; but it would be wrong to regard prefrontal leucotomy as a kind of psychiatric panacea. On the contrary, as things are at present it would be prudent to regard it as the last, rather than the first resort.

(1) *Obsessive-compulsive Neurosis.* Obsessional states can be so severe, intractable and disabling as to justify the use of the term obsessive-compulsive psychosis. The results of psychotherapy, even of deep psycho-analysis conducted over a long period of time, are frequently disappointing. Contrary to the experience of other workers, we have found that electroplexy benefits a certain number of patients. However, when all is said and done, and when all forms of treatment have been tried and found wanting, there is a residuum of patients whose obsessive-tension states are so severe as to render life intolerable not only to themselves but also to their friends and relatives. Prefrontal leucotomy seems at present to be the best method of treatment for this group. After operation, although the patient may not lose his obsessions entirely, he ceases to be emotionally disturbed by them, and is enabled, in consequence, to lead a useful and agreeable life. It is curious to find a person who was previously tormented by morbid scruples, terrifying phobias and ultra-perfectionist drives, now living at peace with himself and his environment.

(2) *Involuntional Melancholia.* The results of electrical-convulsant therapy in this distressing condition are so good (we would go so far as to claim 80 to 90 per cent of successes) that prefrontal leucotomy would not have to be tried on many of these patients. Nevertheless, there are a certain number of acutely agitated, tense, actively suicidal and tormented involuntional patients who either fail to respond to electrical-convulsant therapy or relapse after an initial recovery, and respond less and less well to subsequent course or maintenance dosage. These patients, too, seem well suited to prefrontal leucotomy provided that there is not a high degree of arteriopathy or dementia.

(3) The Schizophrenias. There is not yet much evidence to suggest that prefrontal leucotomy has much effect on that group of disorders regarded as a nosological entity. On the other hand, if a schizophrenic patient is constantly tormented by obsessions, compulsions, terrifying hallucinations and phobic delusions, he is likely to benefit greatly from prefrontal leucotomy.

The view just expressed may be regarded as unduly personal, for many neuro-psychiatrists advocate the operation in schizophrenia much more whole-heartedly. For example: it is claimed by Greenblatt and Solomon at the Boston Psychopathic Hospital that some 40 per cent of chronic schizophrenic patients benefited from operation to the extent of being regarded as cases of "social recovery"; and half of these actually became self-supporting.

(4) Psychogenic Anxiety States. Certain workers are prepared to perform the operation in cases of severe chronic anxiety neurosis in the same way as some treat this condition by means of electrical convulsant therapy. We must confess that we feel a certain repugnance to the treatment of psychogenic anxiety states by either of these methods. Those neuro-psychiatrists who are unable to accept the concept of psychogenesis will doubtless have other views as to the justifiability of "psycho-surgery" in these conditions.

(5) Intractable Pain. It was thought at one time that prefrontal leucotomy would provide the answer to the problem of intractable pain; but, after the first flush of enthusiasm that form of treatment would not appear to have met with universal favour.

Strauss, in dealing with the problem of intractable pain, wrote as follows: "it is impossible to embark on a discussion on pain without being brought up with a bump against the insoluble body-mind problem. All experience, of course, has its origin in sensory data. Sensation becomes perception; percepts are further elaborated into concepts; concepts cluster together to form ideas and ideational constellations; and all these events undergo mnemonic engratization—i.e., the formation of memory traces. So far, it will be noted, I have been able to summarize experience in psychological terms only, without any reference to the material apparatus involved in the process. Nevertheless, it is a common habit of mind to think of pain in physical terms and to draw an artificial distinction between what one is pleased to call 'real' and imaginary pain, oblivious of the fact that all pain, whatever its most peripheral source of origin, is in the final analysis a psychic event.

If the words 'pain' and 'suffering' are mentioned outside any given context it is impossible to decide whether mental anguish is meant or pain arising direct from the body; and this is not a case of one *noumenon* or descriptive category being correct in one context and in another being used as an analogue. The term 'pain' covers both kinds of experience with equal justification, indicating, I would maintain, that, phenomenologically and semantically, mental and physical pain are so closely allied as to be almost identifiable one with another.

If one is compelled to think monistically, it is wiser to regard pain from the psychic aspect and to disregard its material substratum, and to reserve for consideration in neuro-physiological terms the *type* of pain experienced. One can talk of a burning sensation, a boring sensation, a sensation of weight or pressure, a shooting or radiating sensation, a vibrating sensation, and a host of other sensations, all of which can be registered as painful, but not necessarily so. What converts such a sensation into a pain is, in a specially narrow sense, psychic rather than somatic, whatever fibres conduct the original stimulus. In other words, pain is an emotional as well as a sensory experience. Pain divorced from its emotional component is very different from the total experience, as is well shown after leucotomy. The emotional appreciation of pain probably depends on intact memory and unimpaired foresight; therefore leucotomized persons may be said to feel pain in the same way as an undomesticated animal does. When we empathetically suppose that the experience of pain in humans and animals is identical, we are likely to be guilty of the pathetic fallacy.

I believe that there is another important difference between pain as a sensory experience and pain as an emotional one. Pain as sensation is correctly located in the somatic segment in which it is generated in accordance with intact neural pathways".

It would seem that, in many cases, prefrontal leucotomy is able largely to eliminate the "emotional" component of the pain-experience without directly abolishing pain as a sensory datum. The result of successful operation would therefore be to enable a patient to tolerate hitherto intolerable pain without distress of mind. An example of this kind is admirably described by Partridge in his above-mentioned book.

Moral Issues. Many people feel that moral issues are involved in neuro-surgical procedures which modify the personality. Strauss in a review-article summarized the moral theological

position, as it appeared to him, in the following words: "there are, of course, moral-theological factors to be reckoned with in every surgical procedure, but 'psycho-surgery' (which is the horrible term popularized in the United States), and certain other surgical operations, such as those which inevitably result in infertility, call for special consideration. In the last analysis, the moral questions are always identical: there is no direct breach of the moral law if, as the result of a surgical or medical technique carried out with the intention of producing desirable therapeutic results, there are *secondary* undesirable sequelæ. If we apply this moral criterion to prefrontal leucotomy, the same issues emerge clearly. If, in the opinion of the neuro-surgeon and the psychiatrist, it seems unlikely that certain desirable therapeutic ends can be achieved by no procedure other than prefrontal leucotomy, in spite of the fact that there is a risk of certain objectionable secondary sequelæ, there is no violation of the moral law. Successful prefrontal leucotomy (whatever surgical technique is used) inevitably results in the patient stepping down one rung of the ladder of social evolution, for the severing of certain cerebral pathways leads to the impairment of a specifically human quality, namely the capacity for foresight. This change in the personality may be very agreeable for the patient concerned, in so far as it may make for a carefree attitude of gay *insouciance*; but it may indeed be very trying for the patient's family when the pre-psychotic temperament which was characterized by diffidence and kindly consideration for other people's feelings is converted into one of ruthless extraversion. Nevertheless, if a surgical operation on the brain can turn a psychotic patient, whose terrifying hallucinations and generally fragmented personality-structure make him almost unmanageable even in a mental-hospital environment, into an outwardly normal individual who can again take his place in the outside world, the procedure is morally justifiable. Or again: if an obsessive-compulsive neurotic, whose *symptoms* make life intolerable both for himself and his dependents, who has failed to respond to less drastic methods of treatment which have been given a fair trial, becomes relatively normal, even at the cost of a blunting of the finer points of his personality, no moral objection can be raised. It would seem, therefore, that a doctor, in arriving at a decision as to whether leucotomy is indicated in the case of an individual patient, has to consider *social* rather than moral issues".

Summary. The literature dealing with cerebral surgery as it

effects psychiatry is literally enormous. Prefrontal leucotomy is concisely and objectively discussed (together with a good bibliography) by Sargant and Slater in their book, "An Introduction to Physical Methods of Treatment in Psychiatry".

To sum up in general terms—as things are at present, when other forms of treatment have been tried and failed, prefrontal leucotomy is justifiable if the prospect of the relief of anxiety (using the term "anxiety" in its widest sense), after being weighed against the possible post-operative effects, is acceptable to the patient, his relatives, or the institutional authorities responsible for his welfare.

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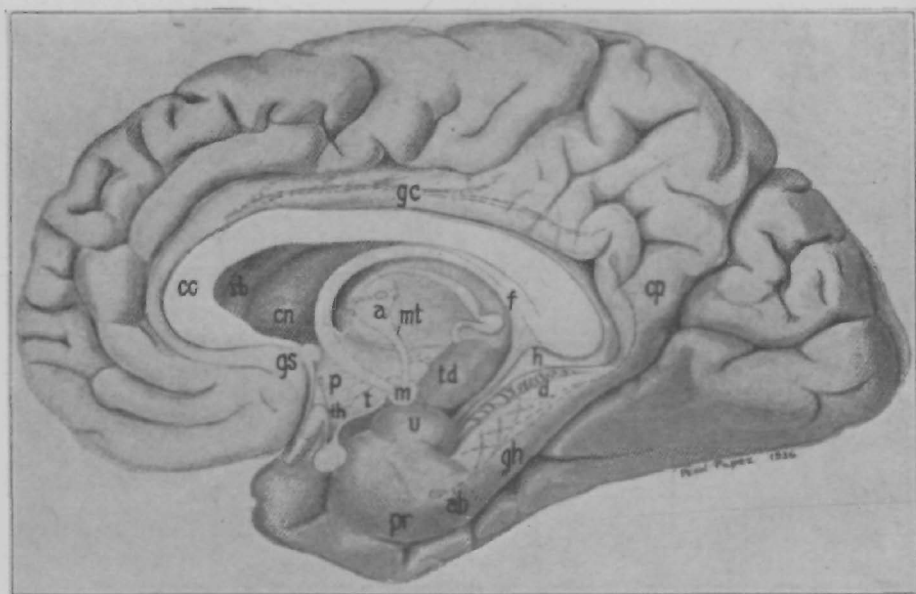


FIG. 2. Medial view of the right cerebral hemisphere, showing the hippocampus and its connection with the mamillary body through the fornix and also the connections of the mamillary body to the anterior thalamic nuclei and thence to the cortex of the gyrus cinguli. In this specimen an unusually large exposed (nude) hippocampus is seen (Papez, 1937).

ABBREVIATIONS

a, anterior nucleus	h, hippocampus nudus
ab, angular bundle	m, mamillary body
cn, caudate nucleus	mt, mamillothalamic tract
cc, corpus callosum	p, pars optica hypothalami
cp, cingulum posterius	pr, pyriform area
d, gyrus dentatus	sb, subcallosal bundle
f, fornix	t, tuber cinereum
gc, gyrus cinguli	td, tractus mamillotegmentalis
gh, gyrus hippocampi	th, tractus hypophyseus
gs, gyrus subcallosus	u, uncus

CHAPTER 3

THE TEMPORAL LOBE

IN this chapter we shall not discuss the auditory functions of the temporal lobe, nor the functions of the dominant temporal lobe in relation to speech, but we shall consider only experimental temporal lobe ablation and recent work on temporal lobe seizures and their surgical treatment.

The Temporal Lobe in Relation to Emotion

In view of the experimental and clinical evidence that lesions of the temporal lobe may cause emotional disorders, this is perhaps the most convenient place at which to consider possible anatomical pathways which may be concerned in emotional reactions, though these are, of course, equally important in relation to the functions of the frontal lobe.

This subject was reviewed by Papez (1937) and subsequent observations have done much to confirm the validity of his schema. He points out that the term "emotion" as commonly used applies to two conditions: a way of acting and a way of feeling. The former is designated "emotional expression"; the latter "emotional experience or subjective feeling". The experiments of Bard have demonstrated that emotional expression depends on the integrative action of the hypothalamus rather than that of the dorsal thalamus or cortex, but for subjective emotional experience the participation of the cortex is essential. Papez illustrates what he believes to be the anatomical basis of emotion in a diagram (Fig. 2). This shows the three principal parts of the hypothalamus. The pars optica is connected through the infundibulum with the pars neuralis of the hypophysis. The tuber cinereum is connected downwards with the lower sympathetic centres. The pars mamillaris is connected by an efferent pathway to the cortex of the gyrus cinguli; it also receives afferent connections from several other sources, the most prominent of which is the fornix from the hippocampal formation. It is the mamillary body which bears the main hypothalamic relations to the cerebral cortex. This, in Papez's view, is a two-way connection consisting of a circuit through the cerebral cortex at the upper level and

through the mamillary body at the hypothalamic level. Thus, impulses may be excited at two points: the cerebral cortex and the hypothalamus. Excitations of cortical origin would pass first through the hippocampal formation and then down by way of the fornix to the mamillary body. From this they would pass upwards through the mamillothalamic tract, or the fasciculus of Vicq d'Azyr, to the anterior nucleus of the thalamus and then by the medial thalamocortical radiation (in the cingulum) to the cortex of the gyrus cinguli.

Papez suggests that the central emotional process of cortical origin is to be conceived as being built up in the hippocampal region and then transferred to the mamillary body whence it reaches the anterior thalamic nuclei and irradiates to the cortex of the gyrus cinguli. The cortex of the cingular gyrus is thus to be regarded as the receptive region for the experiencing of emotion as the result of impulses coming from the hypothalamic region. This circuit would explain how emotion may arise in two ways: as the result of psychic activity and as a consequence of hypothalamic activity. The hypothalamus is accessible to both visceral and somatic sensory impressions from many peripheral sources and emotional colouring may be associated with all kinds of sensory experiences. Papez points out that there are primitive sensory centres in the ventral thalamus which receive terminals from various afferent systems, for example, the optic tract, the acoustic system, the spinothalamic and trigeminothalamic tracts and the medial lemniscus. These nuclei of the ventral thalamus send diffuse fibre connections to the hypothalamus which end in general in the pars optica and the tuber cinereum. These, however, are also connected with the mamillary body. Thus, afferent pathways from the receptor organs split at the thalamic level into three routes: one conducts impulses through the dorsal thalamus and the internal capsule to the corpus striatum; a second conducts impulses from the thalamus through the internal capsule to the lateral cerebral cortex and the third conducts a set of concomitant impulses through the ventral thalamus to the hypothalamus and by way of the mamillary body and the anterior thalamic nuclei to the gyrus cinguli in the medial wall of the cerebral hemisphere.

Since the hippocampus plays an important part in Papez's schema it is interesting that the time-honoured attribution of olfactory functions to this area is now questioned. Brodal (1947) in a study of the olfactory connections states that olfactory

fibres appear to end in the peri-amygdaloid and prepiriform areas of the so-called piriform lobe. It is doubtful if any reach the hippocampus. The hippocampus seems to be an efferent structure sending impulses to the hypothalamus pre-optic region, septal areas and habenula, but most of its outgoing fibres pass through the medial and part of the lateral mamillary nucleus and thence, as Papez states, through the anterior thalamic nucleus to the cingulate gyrus.

Experimental Removal of the Temporal Lobes

Kluver and Bucy (1939) have described the results of bilateral temporal lobectomy in the rhesus monkey. One of the most common symptoms was a disorder of behaviour termed by the authors "psychic blindness", because they believe that it indicates that the ability to recognize and detect the meaning of objects on the basis of visual criteria alone is either lost or seriously disturbed, although the animal exhibits no, or at least no gross, defect in the ability to discriminate visually. The monkeys showed a strong tendency to approach both animate and inanimate objects without hesitation, even objects which previously called forth avoidance reactions, extreme excitement or other forms of emotional response. Objects were picked up indiscriminately, either one after the other or, using both hands, two at a time, all available objects in general being examined. There was a strong tendency to examine all objects by the mouth. This oral examination consisted in putting the object into the mouth, biting gently, chewing, licking, touching with the lips and smelling by holding the object before the nostrils. The reactions of the monkeys made it appear to the observer as if the animals were actuated by some compulsory or irresistible impulse to which the authors applied Wernicke's term "hyper-metamorphosis". Though the operations in some cases caused some visual field defect the authors did not consider that these could explain the symptoms, and no disturbance of auditory function was detectable.

Profound emotional changes were observed or in some cases the complete absence of all emotional reaction, in the sense that the motor and vocal reactions generally associated with anger and fear were not exhibited. Sexual activity, however, in all its forms, autoerotic, homosexual and heterosexual, was greatly heightened.

The characteristic symptoms of complete removal of both temporal lobes did not appear after bilateral removal of the first temporal convolution, bilateral removal of the second and third

temporal convolutions, severing the connections between the temporal and the frontal lobes, or severing the connections between the temporal and occipital lobes. The symptoms did not appear either after unilateral temporal lobectomy, except that there was in some cases a change in the direction of greater tameness. Differential reactions to visual stimuli established pre-operatively were seriously disturbed after bilateral temporal lobectomy, but it was possible to re-establish these responses by training. The ability to generalize in responding to visual stimuli did not seem to be impaired.

Though the authors describe the principal disturbance of function in these monkeys as "psychic blindness", it is by no means easy to decide either the precise nature of this disturbance or its relationship to agnosia occurring in man. Perhaps the most useful conclusions which can be drawn from these observations for the study of disorders of the human temporal lobe are the two broad generalizations that bilateral temporal lobectomy in monkeys causes a profound disturbance (1) of the appreciation of external reality and (2) of the emotional life.

Temporal Lobe Epilepsy

The association of peculiar psychological disturbances with lesions of the temporal lobe has been well known since Hughlings Jackson first drew attention to it. These states have recently been studied, particularly by Penfield and his collaborators, who have had opportunities of observing the effects of electrical stimulation of the temporal cortex, and of correlating the results obtained with the symptoms of epileptic attacks believed to originate in this lobe, (Penfield and Erickson, 1941, Penfield and Jasper, 1947, Penfield and Rasmussen, 1950, Penfield, 1952, Penfield and Jasper, 1954, Gastaut, 1953).

(1) **Hallucinations.** It is a common experience for a discharging lesion of one temporal lobe to cause hallucinations which may implicate any sensory modality. The commonest is certainly the well-known olfactory hallucination. Gustatory hallucinations are also not uncommon, and the patient may find it difficult to decide whether he is experiencing a taste or a smell. Auditory hallucinations may also occur.

Visual hallucinations are of many kinds, and may consist of human or animal figures, sometimes of lilliputian size, or of complex scenes which may actually represent a remembered episode in the patient's past life. There is a tendency for the same

hallucination, or the same kind of hallucination, to recur in each attack. Penfield and Rasmussen describe a girl aged fourteen who suffered from epileptic attacks. The aura of each attack was the revival of a complex scene which represented an experience which had actually occurred to her when she was seven years old. Stimulation of the temporal lobe in this patient produced a variety of auditory and visual hallucinations including complicated visual hallucinations like the aura of her attacks. Hallucinations arising out of temporal lobe disturbances are often accompanied by a strong sense of fear.

(2) **Perceptual Illusions.** An epileptic discharge originating in the temporal cortex may also produce perceptual illusions during which the patient continues to be aware of his environment, but there is an alteration in his interpretation of what he sees or hears. Common forms of such perceptual illusions described by Penfield and Rasmussen are (1) disordered visual perception, for example, macropsia or micropsia; (2) a similar alteration in auditory perception, sounds seeming suddenly louder than they should.

(3) **Disorders of Recognition and Memory.** Although Penfield and Rasmussen speak of abnormal feelings of familiarity as illusions, it is perhaps more appropriate to consider them as disturbances of recognition. The illusion of familiarity may assume various forms. The "déjà vu" phenomenon is common, the patient feeling that he has previously experienced what he is experiencing at the present time. The same illusion of familiarity may attach itself to the hallucination; for example, the patient may say: "I see a figure. I know it is familiar to me, but I cannot say who it is." Finally, the element of recognition may form part of a genuine revival by memory of a past experience. According to Kinnier Wilson (1928) such revival may be very extensive.

(4) **Dreaming.** The close relationship between hallucinations originating in the temporal lobe and dreaming is indicated by Hughlings Jackson's use of the term "dreamy state". The patient will often describe the experience as being like a dream. Moreover, as in the case cited by Penfield and Rasmussen, the remembered experience which figures as the content of the hallucination during an attack may also occur independently as a dream with the qualities of a nightmare. Vivid and unpleasant dreams may themselves be a symptom of a lesion of the temporal lobe.

(5) **Disordered Sense of Reality.** During a temporal lobe seizure the patient's sense of reality may be disordered so that

either he feels he himself is unreal (depersonalization), or he has a similar feeling with respect to his environment (derealization).

(6) **Clouding of Consciousness.** Many of the symptoms described above involve some impairment of normal awareness of the external world. This may reach any degree of severity. The patient, though behaving in an automatic fashion, as described below, may be very incompletely aware of what is going on around him, or an attack may culminate in complete unconsciousness.

(7) **Psychomotor Epilepsy.** The term "psychomotor epilepsy" has come to be applied to a type of attack which is believed usually to originate in the temporal lobe and in which clouding of consciousness is accompanied by automatic behaviour of a fairly highly organized kind, but unrelated to the circumstances of the moment (see page 61). Penfield and Flanigin (1950), Jasper *et al.* (1951) and Hill (1953) all point out that if the term "psychomotor epilepsy" implies automatism, its origin is not limited to the temporal lobe, and it characterizes not more than 50 per cent of the attacks which do arise there.

(8) **Motor Accompaniments of Olfactory and Gustatory Hallucinations.** These are motor activities occurring at a lower level of organization than the motor automatisms just described and particularly apt to occur in association with hallucinations of smell and taste, being the movements which anatomically and physiologically are specially related to these senses, namely, movements of smacking the lips, chewing and swallowing. Such movements, together with olfactory hallucinations and clouding of consciousness, may be the sole disturbances of function constituting an attack originating in the temporal lobe.

The Surgical Treatment of Temporal Lobe Epilepsy

The recent advances in our knowledge of epileptic attacks originating in the temporal lobe has led to their treatment by the surgical removal of the area of abnormal brain held to be responsible.

The Electro-encephalogram before and after Surgery. The general characteristics of the electro-encephalographic abnormalities associated with temporal lobe seizures are described elsewhere in this book. Jasper, Pertuiset and Flanigin (1951), Merlis (1953) and Hill (1953) have published the results of such studies with special reference to the effects of operation. Jasper, Pertuiset and Flanigin compare the results of pre-operative and post-operative electro-encephalographic studies made on 91

patients operated on for temporal lobe seizures. In about three out of four patients there was clear evidence in the pre-operative electro-encephalograms of a focus of onset in one temporal region. In such cases the surgical excision of the epileptogenic lesion, guided by the cortical electrogram, resulted in decided improvement or fewer seizures in about two out of three cases. In about 25 per cent of cases the pre-operative electro-encephalogram did not show a consistent unilateral focus of epileptiform discharge, but, rather, revealed a focus shifting from side to side, or bilaterally synchronous discharges. Prognosis was poor after unilateral temporal lobe excision in such cases. Merlis (1953), however, states that in his material with repeated sleep-studies it was possible to demonstrate bilateral foci in up to 85 per cent of cases, though it might take as many as six sleep records to demonstrate the focus on both sides. His experience was that ablation of the anterior portion of one temporal lobe might control the seizures, although the spike focus in the anterior part of the opposite temporal lobe was still present. Hill (1953) points out that in many patients the electro-encephalogram is normal until the patient is put to sleep and basal electrodes used. The focus may then be single or multiple, unilateral or bilateral, on the cortex of the convexity, buried in the Sylvian fissure, or only seen beneath the anterior part of the sphenoidal electrode—in which case it may arise in the uncus or hippocampus. The best results of surgery are to be obtained in those patients with strictly unilateral, single foci. A clear relationship between recovery from the seizures and improvement in the post-operative electro-encephalogram was observed. A similar correlation was noted by Jasper and his colleagues.

The Effects of Operation upon Mental Abnormality. Hill (1953) discusses the psychological effects of operation in a series of fourteen patients suffering from temporal lobe epilepsy. In the immediate post-operative period of hospitalization up to two months there was an improvement in personality in the form of greater warmth in interpersonal relationships. No significant change was observed in formal intelligence. All but one of the ten patients who became free from seizures showed some degree of improvement in personality. One of the three patients who did not improve showed an increase in libido and behaved in a manner which recalled Klüver and Bucy's description of their monkeys with bilateral temporal lobe ablations. Falconer and Pond (1953) have described the surgical treatment of two patients suffering

from temporal lobe epilepsy with personality and behaviour disorders. Both were children and both were relieved of their epilepsy and temper disorders.

The Nature of the Lesions. Penfield and Flanigin (1950) report the results of operations on sixty-eight patients. In seven cases exploration only was carried out: one patient died after operation. There were five cases of infiltrating tumour which had given no pre-operative evidence of increase of intracranial pressure. In fifty-five cases an atrophic or stationary epileptogenic lesion of the cortex was excised. Included among these stationary lesions were three hemangiomas. The authors tabulate the lesions as follows:—

<i>Lesions</i>	<i>Cases</i>
Area of atrophy (five with cysts)	39
Traumatic scars (one with cyst)	9
Abscess scar	1
Microgyria	1
Unclassified	2
No objective evidence of abnormality	3

Falconer (1953) noted in material excised from his patients sclerosis of Ammon's horn and discusses the significance of this. The classical view has been that such sclerosis is the result of vasomotor and ischaemic changes which occur during the cyanotic stages of major seizures. He quotes Meyer, however, as stating that the brains of many chronic epileptics do not show these changes, even after a long history of severe attacks of grand mal. It is possible therefore that, as has been suggested by Penfield, these sclerotic areas are not the result of the attacks, but their cause. Falconer and Pond (1953) found in their patients described above an unusual calcified lesion associated with increased vascularity and glial sclerosis. Its nature is obscure, but it may be related to the condition described by Penfield and Ward (1948) as "hemangioma calcificans".

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CHAPTER 4

THE PARIETAL LOBE AND SENSATION

THE principal facts about the effects of lesions of the parietal lobes have been known for many years. The chief forms of aphasia, apraxia and agnosia produced in this way were all recognized during the last century. Hughlings Jackson described disturbance of awareness of space and apraxia for dressing, and the phenomenon now known as tactile inattention, extinction or suppression was observed by Oppenheim in 1885. During recent years, however, increased attention has been paid to the disorders resulting from parietal lobe lesions as disturbances of function with the object of throwing light upon their physiological and psychological nature with reference to the different effects produced by lesions of the right and left parietal lobes respectively. The whole subject has recently been exhaustively reviewed by Critchley (1953). In this chapter we shall be concerned only with recent studies of the nature of the disorders of function.

Perceptual Rivalry

It is convenient to begin with a consideration of the phenomenon known as sensory inattention, extinction or suppression, since it has been suggested that an interpretation of this may throw light upon more complex disturbances. The term perceptual rivalry is to be preferred to those just given because it describes what occurs without any implication as to its nature, about which there is not at present any general agreement. The subject has been discussed by Critchley (1949), in a series of papers by Bender and his collaborators (Bender 1945; 1946), Bender and Furlow (1945), Bender and Teuber (1946) (1948), Bender, Fink and Green (1951), Bender, Schapiro and Schappell (1949) and Jaffe and Bender (1952) also by Henson-(1949) and Denny-Brown, Meyer and Horenstein (1952). Perceptual rivalry occurs in its simplest form when a patient suffering from a lesion of one parietal lobe experiences a sensation when a stimulus is applied to the opposite side of the body alone, but fails to experience it when a similar stimulus is simultaneously applied to a spot on the unaffected side of the body which is the mirror-image of that first stimulated.

Though first noted in the tactile sphere the same disorder was subsequently observed in the sphere of vision where it was described as visual inattention.

Critchley has described the various features of perceptual rivalry in the tactile sphere which he calls tactile inattention. It was originally noted when painful stimulation was employed, but other modalities of sensation, including light touch and temperature, may be equally effective. Head and Holmes (1911) observed that in some patients with cortical sensory disturbances if a weight is placed in both hands the patient may gradually begin to think that there is no weight in the abnormal hand. Critchley points out that it is not necessary that the stimuli should be of equal intensity, for when tactile inattention is well marked even powerful pin-pricks are inhibited by faint stimuli applied to the normal side. In the same way a dissimilar stimulus may be effective, as, for example, when a touch with cotton wool on the normal side may suppress the pain of a pin prick applied to the abnormal side. It has been observed both by Critchley and by Denny-Brown and his collaborators that, when an interval of time separates the two contacts, extinction may not occur, provided that the interval between the two contacts is long enough, but if the stimulus is applied to the abnormal side within three seconds of the application to the normal side it will not be perceived. Though commonly the two stimuli are applied to symmetrical areas, and this is probably in general the most effective way of demonstrating perceptual rivalry, the same phenomenon may be elicited by the application of an asymmetrical stimulus to the sound side. Also, when two simultaneous stimuli are applied to the affected side one may prevent the perception of the other. Henson (1949) reported a patient with thalamic over-reaction on the left side which was entirely abolished by the simultaneous application of a similar stimulus to the sound side.

The corresponding visual phenomenon has been studied by Bender and his associates. Bender and Furlow (1945) reported a patient with a gunshot wound of the left occipito-parietal region in whom visual stimuli, originating in the normal homonymous fields of vision, tended to suppress or obscure the image originating simultaneously in the opposite, affected, fields of vision. The more stimulation there was in the normal field, the less the patient saw in the abnormal field. Bender and Teuber (1946) describe various associated abnormalities of visual perception and make the important practical point that in cases of visual perceptual rivalr

widely different visual fields can be plotted in the same patient by using different methods of perimetry. Either tactile or visual perceptual rivalry may occur as the result of a lesion of either hemisphere, and both tactile and visual disturbances may be present in the same patient.

The Nature of Perceptual Rivalry and its Relation to Agnosia and Apraxia

The various terms applied to perceptual rivalry indicate the lack of agreement as to its nature. The term "extinction" throws no light upon this, and "suppression", preferred by Reider (1946) who invokes the suppressor strips in its support, nevertheless lacks a firm physiological basis. There is no doubt that in normal subjects perceptual awareness is considerably influenced by attention, but the evidence as to the effect upon perceptual rivalry of directing attention to the stimulation of the abnormal side of the body is conflicting, and to speak of tactile or visual inattention is not really informative since we know nothing about the physiological basis of attention.

Denny-Brown, Meyer and Horenstein (1952) propose a physiological explanation of perceptual rivalry which, in their view, throws new light upon agnosia. They report a patient with a presumed vascular lesion of the right parietal area who suffered from defect of visual and tactile discrimination on the left side and exhibited the phenomenon of perceptual rivalry. The authors observed that by increasing the spatial area of stimulation it was possible to diminish the patient's perceptual defect and also to abolish the phenomenon of extinction. For example, whereas when two pin pricks were simultaneously applied to symmetrical areas that on the affected side of the body was not perceived, if instead one pin prick was applied to the sound side, and a group of pricks simultaneously to the affected side, the stimulus to the sound side no longer extinguished that to the affected side, which was appreciated as a prick. From this and similar observations the authors infer that the essential disturbance of function resulting from a lesion of the parietal lobe is a spatial one, i.e., it is a failure of discrimination, and they term it amorphosynthesis. They explain the phenomenon of extinction by saying that when two stimuli are simultaneously applied to symmetrical points on opposite sides of the body and one, owing to a lesion of the opposite parietal lobe, is less differentiated than the other, the more differentiated stimulus is perceived. They go on to distinguish

three levels of perceptual disturbance. (1) When perception is disturbed as the result of a lesion of the conducting sensory pathways up to, and including, the optic thalamus, sensory tests are characterized by an all-or-none response. (2) At the level of the parietal cortex the function of morphosynthesis based upon spatial discrimination comes into play. In this respect each parietal lobe functions in relation to the opposite side of the body and there is no functional difference between them. (3) Symbolic functions are normally localized in the dominant hemisphere, a lesion of which causes them to be disturbed on both sides of the body. Failures of unilateral perception produce disturbances of behaviour, but, in the past, according to Denny-Brown and his collaborators, confusion has arisen from failure to distinguish sharply between phenomena resulting from failure of unilateral perception and inability to recognize conceptual schemata whether drawn in outline, pictured in imagery, or conveyed to the patient in speech (agnosia, aphasia). Thus there is no reason to assume the existence of any disorder of the conception of the patient's own body or of extra-personal space or of topographic representation in the patient's mind as the result of a lesion of the non-dominant side, though his behaviour and comprehension may be disordered in relation to all these. The resulting defect of behaviour may appropriately be called an apraxia and Denny-Brown, Meyer and Horenstein's patient showed both constructive apraxia and apraxia for dressing. Nevertheless in their opinion the defect in movement was patently the direct result of failure of perception of the next step in a movement sequence. The loss of visual components of such morphosynthesis in addition to tactile factors is the basis of unawareness of parts of extra-personal space and unawareness of self, without disorder of the concept of space or of the body schema. Such unawareness differs considerably from simple loss of sensation. The defect in motor behaviour resulting from parietal lesions, however, is the result of lessening of adequacy of stimulus for cortical reactions.

Disorientation in Space

Human orientation and disorientation in space is a complex subject which has recently attracted considerable attention. It exemplifies to the full the confusions which arise in so many discussions of organic brain disorders which possess both physiological and psychological aspects. It is not difficult to understand how these confusions have arisen, though the task of eliminating

them is a long and arduous one which has only just begun. Initially we observe that there is something wrong with a patient on account of his behaviour, which includes his own description, or attempt to describe, why he acts as he does. This is the stage of description of symptoms. One patient, let us say, has difficulty in finding his way about, difficulty in writing and difficulty in arranging matches to correspond with a pattern. Another patient has difficulty in recognizing objects, and a third has difficulty in writing combined with difficulty in speaking. So far no great difficulty arises, though it should be noted that the term "difficulty in recognizing objects" is one which might apply to more than one kind of disability. The next stage is reached when, for purposes of convenience, a technical term is applied to the patient's symptoms: thus, the patient who has difficulty in writing is said to be suffering from *agraphia*, while difficulty in constructing patterns from matches is called *constructive apraxia*, difficulty in recognizing objects is called a form of *agnosia*, and so on. Difficulties now at once begin to arise. Two patients have been mentioned, both of whom had difficulty in writing. If they are both said to be suffering from *agraphia* it tends to be assumed that physiologically, and even, perhaps, anatomically, their disorders of function must have something in common, yet, in fact, this may be quite misleading and in one case the difficulty in writing may be due to a disorder of function which underlies the difficulty in making patterns and in finding routes, while in the other case the difficulty in writing is due to a disorder of the function which underlies both it and spoken speech. Similarly the use of the term *agnosia* to describe a variety of symptoms, all characterized by some difficulty in recognition, may be misleading if it is taken to imply that they are characterized by some common disturbance of function in a physiological sense. Furthermore, the use of a term like *agnosia* may be held to indicate that it is the result of a deficit of some activity which can possibly be called *gnosia* and from this it is but a step to the supposition that such functions must be located somewhere in the brain and that their disturbance is brought about by a lesion so placed as to interfere with the localized function. The recent trend of neurological thought in dealing with these problems has been to investigate the disturbance of function in physiological and psychological terms and to see how far, and in what sense, it can then be correlated with the anatomical lesion, and to apply the knowledge thus gained to the criticism of the older concept of the terminology of symptoms.

Varieties of Spatial Disorientation

Human reaction to space involves extremely complex processes. Space itself is an abstract conception derived from the spatial relationships which are observed to exist between objects. Furthermore, the space in which external objects are seen to exist is always orientated in relation to the existing position of our bodies. Psychophysically, therefore, extra-personal space is intimately related to that part of space which is occupied by our bodies. Hence there is a tendency for a lesion of the parietal lobe to disturb our appreciation of external space and of the body at the same time and in the same way. The principal sensory channels by which impulses concerned in our awareness of, and reactions towards, space reach the nervous system are the retinae, the proprioceptors of the external ocular muscles and of the ciliary muscles, the labyrinths, the proprioceptors of the muscles and the joints of the body, including the spine, and especially the cervical spine, and the cutaneous receptors, especially in the soles of the feet and the buttocks. Hearing and the other senses play subordinate parts. We do not, however, experience space for its own sake, but always in relation to actions or potential actions directed towards the objects which occupy it. Awareness of the position of an object, therefore, already as it were sketches out in advance the movements called for by our potential action towards it. Sensation and movement are here so intimately related, as Gooddy (1949) has pointed out, that they are likely to be disordered together by any lesion which disturbs spatial orientation.

It follows from what has been said that, since so many factors contribute to our experience of space, the perception of space, and actions within it, may be disordered by disturbances of function occurring at a large number of points, peripheral as well as central, and in a wide variety of ways. Thus, for example, impairment of tactile discrimination and of appreciation of passive movement in the digits of the hand, resulting from a lesion of the peripheral nerves or spinal cord, interferes to a limited, though important, extent with awareness of the spatial characteristics of objects placed in the hand. Similarly, a disturbance of function of one labyrinth may for the time being grossly disturb awareness of external space and render appropriate action towards it impossible. Usually, however, the term spatial disorientation is reserved for those disturbances of function which occur as a result of lesions of the cerebral cortex or subcortical white matter. Even

so, a large number and variety of symptoms of disordered spatial awareness have been described.

In the visual sphere the simplest form of spatial disorder is metamorphopsia, in which the size, shape and spatial relations of objects are disordered, and in rare instances the visual fields may even be inverted. Localization of objects in visual space may be disordered in any of the three dimensions. Defective visual localization of objects in space may be limited to one hemianopic half-field. It is characterized by inability to appreciate the absolute and relative positions of objects seen, especially in relation to the patient's sagittal plane, and hence to point to them. Bilateral lesions cause much more severe disturbance than unilateral ones. Patients with bilateral lesions cannot find their way around objects when they run into them, set out in the wrong direction to get to objects which they clearly see, and have difficulty in finding their way about and learning the topography of a room. Loss of stereoscopic vision is a rare symptom.

Another form of disorientation is a neglect of one half of space. This is most frequently detected in a patient with a massive lesion in the right parieto-occipital region. Such a patient, when following a familiar route, may tend to turn to the right instead of to the left in error and consequently get lost in familiar surroundings. The same neglect of the left half of space may be shown in a failure to complete the left half of a drawing (Goody and Reinhold, 1952) or of a map. It is likely to be associated with similar symptoms referred to the left half of the body, described below.

In spite of the disabilities already described the patient may be able accurately to describe routes familiar to him and visualize familiar scenes. Loss of this ability, topographical memory, is a disorder independent both of other forms of visual disorientation and of loss of memory for objects. Although in many of the reported cases bilateral lesions have been present, the available evidence suggests that loss of topographical memory is usually the result of a lesion of the dominant hemisphere, though this may be the right one (Paterson and Zangwill, 1945).

Disorders of the Body-Schema

The conception of a body-image or body-schema is by no means new, since it is nearly fifty years since Pick first made a systematic study of imperception of parts of the body, which he called autotopagnosia and from which he developed the idea of a spatial image of the body. Head and Holmes (1920), borrowing the term

schema from Kant, contributed the conception of a plastic and constantly changing unconscious model of the body against which changes in its posture could be recognized. Their conception, though in some respects possibly requiring modification, appears to more useful than the idea of a body-image, since it cannot be maintained that the symptoms of disorder of the awareness of the body are purely, or even primarily, the result of the loss of sensory images. All our bodily activities, and equally our awareness of the body and its parts, are based upon physiological organizations of nervous impulses derived from the proprioceptors of the limbs and trunk, the sensory receptors of the skin, the labyrinths, vision, and the memory traces of similar impulses in the past.

Almost all the studies of disorders of the body-schema have been made in the case of patients with a lesion of the parietal lobe of the right or minor hemisphere. There is some evidence that similar symptoms may occur as the result of a lesion on the left side, but, if so, they are much more difficult to detect. The lesion of the parietal lobe does not operate merely by producing defective appreciation of the position of the limbs on the opposite side, since this may be present without any impairment of the normal mode of perception of that half of the body. Nevertheless, disturbance of the body-schema for the left half does not appear to occur without gross left-sided sensory disturbance. The disorder may exist in varying degrees of severity. Thus, the patient may complain that the limbs on the left side of the body feel as though they were absent, although he knows that they are still present; or he may maintain that they are absent, and yet, when his attention is directed to them, he may admit that his belief was mistaken; or, on the other hand, his delusion of their absence may be complete and unshakable by evidence to the contrary, in which case he may explain the appearance of his own arm by saying that it belongs to the patient in the next bed, or to some other person, or that it is a snake or some other foreign object. A patient who denies the existence of the left half of his body will, if it is hemiplegic, also deny that it is paralysed. Less frequently hemiplegia is denied although the existence of the limbs is still admitted.

The site of the lesion responsible for disorders of the body-schema arising out of damage to the minor hemisphere is discussed by Nielsen (1938), Hagen and Ives (1939), Roth (1949) and others. It is usually situated in the cortex and subcortical white matter of the right supramarginal and angular gyri. This region lies between the postcentral convolution, which is concerned with the

awareness of deep sensibility on the opposite side of the body, and the visual cortex, which represents the left homonymous half of the visual fields in which the opposite half of the body is normally visually perceived. It also includes a cortical centre for vestibular impulses. It appears that a subcortical lesion is effective if it destroys the thalamo-parietal peduncle, and there is some evidence that the syndrome may result from a lesion of the optic thalamus itself. The particular thalamic nucleus concerned is unknown, but Roth suggests that the pulvinar may be important.

Unawareness of Disease

Unawareness of disease, or anosognosia, has been known for over half a century, but the recent awakening of interest in the body-schema has stimulated investigation of this peculiar symptom and recent publications on the subject include those by Redlich and Dorsey (1945), Sandifer (1946) and Roth (1949). The commonest example of anosognosia is unawareness of hemiplegia, which has already been mentioned in the discussion on imperception of the left half of the body. Usually this is associated with one of the forms of disordered awareness of the left half of the body already described, but this is not always the case since the patient may deny his hemiplegia, though fully aware of the existence of his paralysed limbs. This is then a defect of judgment, and Sandifer stresses the importance of the presence of an intellectual defect in addition to the lesion of the afferent pathways. Anosognosia for blindness was the first symptom of this kind to be described. Denial of deafness may occur in the same way, and the common unawareness of the patient with jargon aphasia that he is talking jargon is a comparable symptom.

Rubins and Friedman (1948) have recently reported four patients suffering from the condition described by Schilder and Stengel as asymbolia for pain. In this condition the degree of response to a painful stimulus varies from complete denial of the pain to a little exclamation and some partial movement of avoidance. Threatening gestures fail equally to produce a protective reaction. The fundamental disorder in these cases, though not fully understood, appears to be a failure to integrate the awareness of the pain with awareness of the body-schema. Asymbolia for pain in some respects recalls the phenomenon of tactile inattention, and Critchley (1949) mentions a possible relationship between asymbolia for pain and bilateral tactile inattention.

The Nature of Disorders of Awareness of Space and of the Body-Schema

As stated earlier in this chapter we are not yet in a position to offer any adequate and comprehensive explanation in either physiological or psychological terms of the disorders of awareness of space and of the body-schema which we have been describing. Denny-Brown, Meyer and Horenstein (1952) have proposed a conception which, though not perhaps completely satisfactory, is a stimulating criticism of earlier ideas and a constructive substitute for them. The main features of their hypothesis are set out above. They attribute the spatial disturbances referred to the left side, from which their patient suffered, to amorphosynthesis resulting from the lesion of the right parietal lobe. The disorders of visual spatial perception in their view are attributable to visual amorphosynthesis and a similar disorder of function is held to explain the patient's attitude towards the left side of the body, which was treated as if the affected side and half of space did not exist. The authors also consider that anosognosia when it occurs is derived from the same physiological disorder, for, they state, "it lacks the conceptual features of pure agnosias, is one-sided, and is regularly associated with cortical sensory loss, i.e., with amorphosynthesis. Its occurrence with large parietal lesions indicates that a combination of visual with other elements of amorphosynthesis is necessary, and that a loss of cortical sensation in the limbs is not necessarily maximal." Amorphosynthesis is thus regarded as a disorder of function occurring at a higher level than mere interference with sensory conducting pathways, but at a lower level than symbolic or conceptual functions which, it is held, are related to the dominant hemisphere, while in respect of morphosynthesis each hemisphere functions in relation to the opposite side of the body. Denny-Brown and his colleagues therefore believe that amorphosynthesis can occur while the concepts of the body and of parts of the body are unaffected.

These views, interesting as they are, illustrate the difficulties which beset this subject. Amorphosynthesis is a physiological conception, for there is no such psychological process as morphosynthesis. Such an idea, which may prove valuable in the interpretation of the physiological disturbance, is then set up in opposition to the idea of agnosia which is a psychological conception. This antinomy, which has no logical basis, leads to the conclusion that a patient who behaves as though the left half of his body does

not exist, and who denies the existence of paralysis in it, is not suffering from a conceptual disorder. Nevertheless, it is only by pressing on with similar physiological and psychological interpretations that we can hope to clarify our ideas in this field.

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CHAPTER 5

CONSCIOUSNESS AND UNCONSCIOUSNESS

WE are perhaps apt to take both consciousness and unconsciousness for granted when they occur normally as states of waking and sleeping. Disorders of consciousness, however, present some of the most fascinating problems of the borderland between physiology and psychology, neurology and psychiatry—a region upon which recent researches have thrown considerable light from various angles.

What, then, do we mean by consciousness? “Consciousness is not something which we can define in terms of anything else: we can only indicate its meaning denotatively, that is by pointing to instances of it. When I hear a sound or see a colour, remember something, experience an emotion or think, I am conscious. Consciousness is a quality which these states, which we call conscious states, have in common, but there is no reason to suppose that it exists independently of them. ‘There is no such thing as consciousness apart from conscious states, any more than there is redness apart from red objects’” (Brain, 1950). Nevertheless, many writers, both clinicians and physiologists, speak of consciousness as though it were a function existing independently of those individual conscious states which are characterized by it. No doubt the reason for this is that both types of investigator are familiar with conditions in which consciousness appears to be disturbed as a whole, and this is reflected in current usage since when we speak of a patient as suffering from a disturbance of consciousness we usually mean that he is unconscious or partially conscious, that is, we use the term unconscious to describe what we regard as a disturbance of a global function and we do not usually speak of a pain or a paræsthesia as a disturbance of consciousness, though such a statement would be perfectly accurate. Hence experience leads us to make a distinction between disorders of consciousness as such and disorders of the content of consciousness, though, as we shall see, this distinction is by no means an absolute one.

Clinically we encounter three main types of disorder of consciousness. (1) Paroxysmal and brief attacks of disturbance or loss of consciousness, as in epilepsy and syncope. (2) Persistent

and prolonged loss or impairment of consciousness, as in states of stupor and coma, and (3) disorders of the content of consciousness. As already stated, this last category covers a very large field of phenomena and might be taken to include pains and paræsthesiæ. Nevertheless in practice a distinction is commonly drawn between what might be termed focal disturbances of the content of consciousness, such as a pain, and those which, though manifesting themselves in the content of consciousness, nevertheless seem to arise from interferences with processes fundamental to consciousness in itself. This is exemplified by the hallucinatory states associated with sleep disturbances, produced by drugs or by disease, or occurring spontaneously.

Until twenty-five years ago investigations of such disorders of consciousness depended almost entirely upon clinical observation alone. Then came electro-encephalography which led to the discovery that abnormalities of consciousness might be correlated with abnormal cortical rhythms, and different kinds of disorder of consciousness with specific types or localizations of electro-encephalographic abnormality. Electro-encephalography also opened up a new field of anatomical and physiological investigation. Clinicians, especially neurosurgeons, observed that lesions in certain situations were liable to cause either prolonged or paroxysmal disturbances of consciousness, which in some cases could be correlated with electro-encephalographic changes. They also observed the nature and extent of lesions which did not disturb consciousness. Electro-encephalography added a new and valuable technique to the methods of neurophysiology. The neurophysiologist studying disturbances of consciousness experimentally has used electro-encephalography to detect the passage of nervous impulses aroused by sensory stimuli through the brain stem and their arrival at the cortex, to study the cortical electrical changes associated with sleep and waking, and to investigate the effects upon both of these of electrical stimulation and destructive lesions at various levels. Finally, the experts in clinical electro-encephalography have discovered ways of inducing abnormal electrical rhythms in the conscious subject and studying their effect upon consciousness.

The Rôle of the Central Reticular Formation of the Brain Stem in Consciousness

Recent work by Magoun and his collaborators has established the importance in monkeys and man of the central reticular formation

of the brain stem in relation to the maintenance of consciousness. Previous work on the cat (Lindsley, Bowden and Magoun, 1949) had already pointed in this direction. French, von Amerongen and Magoun (1952) studied electro-encephalographically alterations in the electrical activity of the brain-stem and the cortex which occurred in monkeys as the result of various forms of sensory stimulation. They demonstrated that sensory stimuli excited not only the well-established laterally-placed centripetal pathways, but also a medially-situated system in the brain-stem. This area extended at least from the lower border of the pons to the ventro-medial thalamus, and excitation of it caused cortical desynchronization characteristic of the change in the electro-encephalogram from drowsing to wakefulness. This investigation was carried further by French, Verzeano and Magoun (1953). Using similar methods they demonstrated that sensory stimulation aroused two afferent pathways, one the familiar laterally-placed lemnisci and the other through the central reticular formation. Electrical potentials in the former showed rapid conduction, segregation according to sensory modalities, and discrete cortical projection to the primary receiving areas. The medially-conducted potentials, on the other hand, showed slower conduction, common transport for all modalities, shown by the mutual influence of suitably timed stimuli of different sensory qualities, and distribution to wide areas of cortex by diffuse projection from the medial centrum and the intralaminar nuclei of the thalamus. All sensory modalities were represented in the central reticular system. The thalamic nuclei just mentioned irradiate impulses to the associational thalamic nuclei and to the associational areas of the cortex which in the monkey include the frontal associational areas, both the cingulate and orbital as well as the lateral ones, and there is also irradiation to the primary receptive areas of the cortex. The authors suggest that the lateral lemniscal pathways are concerned with the conduction of sensory impulses which contribute to the perception, recognition, localization and qualitative discrimination of stimuli, while the medial pathways are concerned in initiating and maintaining the conscious state and providing in this way the necessary background of activity without which no integrative sensory, motor or adaptive behaviour is possible. In favour of this view is the fact that the depression or destruction of the central reticular formation renders the subject unconscious.

This was shown by French and Magoun (1952) who made electrolytic lesions in the central cephalic portion of the brain-stem

in monkeys. They found that the destruction of this area was not compatible with survival, while less extensive lesions resulted in akinesia and hypersomnia, and a condition simulating coma in man. The electro-encephalograms were characterized by hypersynchrony which did not respond to sensory arousal stimuli.

Disorders of Consciousness Resulting from Lesions of the Brain Stem and Optic Thalamus

French (1952) has studied the situation of the brain lesions associated with prolonged unconsciousness in man. Five cases are described. In three the lesions were in the reticular activating system in the cephalic part of the brain-stem. In one the dorsal portion of the thalamus was affected and in one the entire cortical mantle was involved. French reviews the literature on the relationship between the brain-stem and the hypothalamus and consciousness. Cairns (1952) studied the disorders of consciousness produced by lesions of the brain-stem. He pointed out that consciousness is never disturbed as a result of a lesion at the upper end of the spinal cord. There is, however, a considerable body of evidence that disturbance of the medulla oblongata, as well as of the pons, can produce loss of consciousness which is usually sudden in onset and deep, and in many cases of grave prognostic significance. Although this loss of consciousness is usually associated with some disturbance of breathing or circulation Cairns considered that the clinical evidence was fairly strong that the loss of consciousness preceded the respiratory and circulatory symptoms.

Cairns observed unconsciousness in some form in 37 out of 73 verified cases of tumour involving the upper brain-stem or optic thalamus. The disorder of consciousness might be intermittent or continuous. The chief forms of intermittent loss of consciousness were tonic fits and attacks of minor epilepsy. Cairns has observed that unconsciousness may be readily induced by manipulation of the anterior part of the third ventricle and that interference with the lamina terminalis may produce not only stupor and attacks resembling petit mal, but also fits of other kinds. According to Cairns continuous unconsciousness with lesions of the upper brain-stem and thalamus may take the form of (1) coma with decerebrate rigidity; (2) hypersomnia; (3) akinetic mutism; and (4) coma with hyperthermia. Though these forms are distinct, one may pass into another. The state of akinetic mutism had previously been described by Cairns and his colleagues in a patient with an epidermoid cyst distending the region of the third ventricle.

Cairns says that in this patient the state resembled sleep, in being associated with general muscular relaxation and in the promptness of waking when the cyst was emptied. It differed from sleep in that her eyes remained alert to normal stimuli and in not disappearing when strong afferent stimuli were applied. EEG. records while the state of akinetic mutism was present showed very large, slow, irregular delta waves (two per second) over the whole scalp, with bursts of slightly faster regular sinusoidal waves. The records to some extent resembled those of normal sleep. After aspiration of the cyst the normal pattern of EEG. reappeared, but, as in a patient with hypersomnia, this improvement lagged somewhat behind the clinical improvement.

The Thalamo-Cortical Connections and Consciousness

Jasper and Droogleever-Fortuyn (1947) reported that by rhythmical electrical stimulation of a small area about two square millimetres in size in the medial intralaminar region of the thalamus in cats it was possible to reproduce all the electroencephalographic features of petit mal. Thus a small area in the anterior portion of the massa intermedia yielded on stimulation a bilaterally synchronous three per second wave-and-spike discharge in the frontal areas. Their observations suggested that this region of the thalamus did not normally maintain a close control over the independent thalamocortical systems related to specific thalamic nuclei, but that it was capable of synchronizing the spontaneous rhythmical activity of these various semi-independent systems into a rhythmical beating of all thalamo-cortical systems and probably other cerebral structures as well. Penfield and Jasper (1947) in a study of what they then described as "highest level seizures" observed that the anterior frontal regions are different from the rest of the human cortex in that seizures beginning there obliterate consciousness from the very onset and yet the removal of these areas does not cause unconsciousness. They define "highest level seizures" as attacks which primarily disturb consciousness. Minor attacks (petit mal) produce absence of consciousness, not alteration of its content, with little or no bodily manifestation of change. In a severe attack the initial loss of consciousness is followed by a symmetrical generalized convulsion. An epileptogenic lesion of the mesial or inferior aspect of a frontal lobe, although it is unilateral, may produce bifrontal synchronous discharges which suggest that such a unilateral focus fires directly into a more centrally placed area of grey matter which in turn converts the

unilateral discharges into outgoing bilateral discharges which tend to have a two to three per second rhythm, so that the evidence suggests that this area, which Penfield and Jasper call "the highest level", lies in the diencephalon and perhaps mesencephalon, and that it has a somewhat more direct connection with the anterior portions of the frontal lobes on both sides than with other portions of the cortex. This area must be the source of origin, or the integrating centre for, the bilaterally synchronous electrical discharges which are characteristic of petit mal or highest level seizures.

Penfield and his collaborators have recently returned to the study of these problems and have sought to integrate their own observations with the experimental work of Magoun and his fellow-workers. Jasper and Ajmonie-Marsan (1952) believe that it is now possible to sketch the broad outlines of a working hypothesis of possible mechanisms of integration in thalamo-cortical and cortico-thalamic projection systems, which is based upon a continuance at the thalamo-cortical level of the distinction between the two afferent systems described in the brain stem by Magoun and his collaborators. On the one hand the sensory nuclei of the thalamus are related to the corresponding sensory areas of the cortex to which they project strong monosynaptic rapid relays of relatively fixed patterns of impulses. These thalamo-cortical connections are concerned with the well-known cortical functions of discrimination of space, time and intensity. Synapses in these circuits are relatively stable and are resistant to anaesthesia and to other factors which affect the level of consciousness and responsiveness of the organism. The first cortical neurones to respond to volleys from the sensory nuclei, namely, those giving rise to surface-positive cortical spikes, also participate in the stable portion of these specific sensory systems. In addition to this specific sensory conducting system there is a diffuse projection system from deeper structures to the cortex which appears to be a mechanism capable of regulating the elaboration of afferent impulses within the sensory receiving areas. This diffuse projection comes, at least partially, from the reticular formation of the diencephalon and mid-brain. From the thalamic portion of this system the regulatory action may be concerned in the central control of affective processes. There is evidence that this activity of the central reticular formation is itself influenced by what is happening in the cortex, probably through cortico-thalamic projections.

Penfield (1952) has reconsidered the conception of "highest level

fits" in the light of this new work. He now proposes the word "centrencephalic" to identify that system within the diencephalon, mesencephalon and probably rhombencephalon which has bilateral functional connections with the cerebral hemispheres. He analyses the clinical characteristics of three types of epileptic automatism which he distinguishes as (1) temporal automatism, (2) frontal automatism and (3) petit mal automatism.

Since automatism originating in a discharge from one frontal lobe is rare, the common varieties are temporal automatism and petit mal. Automatism following spontaneous discharge from one temporal lobe leads to a varying degree of lack of understanding. At the beginning of an attack the patient may smack his lips and swallow. He may fumble about and he often examines his own clothing. He may then move about as though he neither heard nor saw, and as though he could not speak, but a little later he may reply when addressed and may even obey commands momentarily. He may then continue to carry out a plan which he had decided upon before his attack, or he may embark upon a repeated performance which has come to be his habit while in such a state. Such patients resent interference vigorously and sometimes even dangerously. All patients in this state will have an amnesia for the duration of the automatism although they may subsequently remember a sensation, or dream, that preceded it during the preliminary localized cortical discharge. In petit mal automatism, which is ordinarily quite brief, there is usually a complete absence of anything except continuing activity, such as walking or the maintenance of a posture. There is no warning at the beginning of the attack and if there is movement at all it is a quick, symmetrical jerk of the extremities or a fluttering of the eyelids with upward turning of the eyes. In both type of automatism there is complete amnesia for the attack.

Penfield draws certain conclusions, which he admits are largely hypothetical, from the different features of the two main types of epileptic automatism. He believes that they indicate the presence of two cerebral mechanisms. The first, which he calls the A mechanism is used to record the current perception and depends upon the integrity of grey matter within the centrencephalic system and upon associated activity in the temporal cortex and probably upon associated activity in the extramotor grey matter of the frontal cortex. Interference with the A mechanism does not necessarily disturb the B mechanism which is used in the integration of the sensory and motor systems, the acquired skills of speech

and manual dexterity, and in recollection of past experience. It is the B mechanism which, in Penfield's view, is responsible for temporal automatism, while the disorder of the A mechanism in such circumstances explains the patient's amnesia. There is, however, no evidence that the A mechanism can continue to function when the B mechanism is out of action. In other words no patient shows evidence of continued understanding during, or preserves memory after, a major generalized convulsion. Furthermore, Penfield concludes that the fact that there are two kinds of epileptic automatism associated with amnesia indicates that there are two units functioning within the A mechanism. Frontal automatism, which in his view appears to be identical with petit mal, is, he suggests, the outcome of a disturbance in the centrencephalic portion of the frontal subdivision of the A mechanism, while temporal automatism usually results from a discharge that originates in the cortical portion of the temporal subdivision of the A mechanism.

Sleep

Since we know that conscious perception, all except the cruder forms of sensation, is a function of the cerebral cortex, it is reasonable to infer that during sleep the activity of the cortex is depressed. This view has been confirmed by the study of the behaviour of cortical electrical rhythms during sleep by means of electro-encephalography.

The Electro-encephalogram During Sleep. The EEG. has been studied during both normal and pathological sleep by several workers. According to Davis, Davis, Loomis, Harvey and Hobart (1937), there are five stages in the process of falling asleep. Briefly, as sleep deepens there is a transition from the normal alpha wave through a phase of bursts of more rapid waves to the development of slow, random waves known as "delta waves" of a type present in various conditions in which the cerebral cortex is in a state of profound inactivity. Dreams were found to be associated with a burst of alpha waves during the second stage of sleep. Blake, Gerard and Kleitman (1939) describe a gradual trend from hour to hour in spite of momentary fluctuations, the sequence of waves being alpha + delta, delta, null, and intermittent alpha, as the night progresses. As sleep increases in depth, delta waves appear before the alpha waves are gone: later, the delta waves disappear before the alpha waves return. It was found that correlation could be established between the subjective state of the sleeper

and potential pattern recorded by the EEG. When the subject was awakened at varying intervals during the night it was found that dreaming occurred most of the time, though it was minimal in the second quarter.

Bremer (1937) found that in animals the EEG. during normal sleep was identical with that present in an animal which had been decerebrated by transection of the brain-stem.

Loomis, Harvey and Hobart (1936) found that, electro-encephalographically, hypnotic sleep did not resemble normal sleep. They found that the alpha rhythm was somewhat slowed, but it was still suppressed by a painful stimulus even though this was applied to an area which, it had been suggested to the subject, was anæsthetic. It is of interest, however, that the rhythm could be stopped and started by the suggestion to the subject that he could or could not see.

The electro-encephalogram in narcolepsy shows little definite abnormality (see p. 220). Walter, Griffiths and Nevin (1939), in a case of pathological somnolence due to a tumour of the hypothalamus, found an electro-encephalogram resembling that occurring in deep, natural sleep.

Blake, Gerard and Kleitman (1939) say that hypersomnia is associated with delta waves occurring at higher levels of consciousness than is the case in normal sleep.

The Physiological Nature of Sleep. The hypothesis that inhibition is an important element in normal sleep is by no means new, having apparently been first proposed by Brown-Séquard and discussed by subsequent authors. Pavlov (1927), however, first brought this conception out of the realm of hypothesis, and substantiated it by experimental data. Actually, the hypothesis was forced upon him as an explanation of his experimental observations, for his theory of sleep was formulated to explain the unexpected onset of sleep occurring in dogs during the course of his experiments. When an indifferent stimulus is suddenly presented to a dog, it will dispose its peripheral receptors in such a way as best to attend to it. Thus, if an indifferent auditory stimulus be suddenly applied, the dog will cock up its ears and turn its head in the direction of the sound. This reflex has been appropriately called the *orientation reflex*. If the same stimulus be repeated several times at short intervals and any other distracting sounds be completely excluded, the animal loses interest and fails to orientate. If this repetition at short intervals be kept up for any length of time, the animal becomes drowsy and eventually

falls asleep, provided that extraneous stimuli are still carefully excluded. The failure of the orientation reflex is regarded as an example of inhibition, and the onset of sleep is explained by the cortical spread of the inhibitory process in the absence of any excitatory process to check its irradiation. The indifferent stimulus first attracts attention because it may convey some special meaning requiring an appropriate response (i.e., it may be of biological importance). When the stimulus recurs repeatedly and "nothing happens", the stimulus is recognised as "meaningless", attention is withdrawn and the orientation reflex is inhibited. The hitherto indifferent stimulus with its "meaning of 'no-meaning'," has by repetition temporarily acquired a negative sign.

If in the course of experiments involving delayed and trace reflexes the period of delay between the conditioned stimulus* and the presentation of food is protracted beyond a certain limit, inhibition of the conditioned reflex occurs, followed by profound sleep. If the period of delay is rather less prolonged during such experiments, it frequently happens that the dog goes to sleep during the latent period and then wakes up to give a strong reflex response. Here, again, we are to account for the onset of sleep in terms of internal inhibition. We have seen inhibition pass into sleep, and Pavlov deduced from this that sleep and inhibition are identical, inhibition being "local sleep"—that is, sleep confined to certain centres—and sleep (in the ordinary sense of the term) being inhibition of wide cerebral spread. It is also possible to observe the transition from sleep into inhibition by reversing the last-quoted experiment. That is to say, that if the period of delay be rather long from the start and then be very gradually reduced, the dog will from the onset show signs of torpor and will become, *pari passu* with the shortening of the delay period, more and more lively, finally giving a vigorous delayed conditioned reflex uncomplicated by somnolence.

Pavlov's theory may be criticized on the ground that even if sleep coincides with internal inhibition it is not necessarily identical with it. For example, if there is a waking centre, a question which will be discussed below, the extension of inhibition to the waking centre might produce sleep without sleep necessarily being identical with an extension of inhibition over the whole cerebral cortex. Kleitman (1929) proposes a different view, namely, that sleep is an easily reversible inactivity of the highest functional centres of the cortex which is due to a functional break

*Even painful stimuli can be employed in this way to produce sleep.

resulting from a decrease in afferent impulses from the sensorium, especially from proprioceptors stimulated by muscle tonus. Bremer (1937) states that in an animal decerebrated by transection of the brain-stem the electro-encephalogram of the cerebral cortex is identical with that found during normal sleep.

Much clinico-pathological and experimental evidence in the past has indicated that lesions in the neighbourhood of the posterior hypothalamus and aqueduct of Sylvius lead to states of abnormal sleepiness. Consequently it has sometimes been termed a sleep centre, but it has also been pointed out that since its destruction causes sleepiness it would better be described as a waking centre. Recent experimental work has considerably clarified the relationship between this part of the brain and sleep. Magoun (1952) discusses the importance of the ascending reticular activating system in this connection.

The electrical changes in the cortex associated with sleep have been described above. If a sleeping animal is awakened suddenly, as, for example, by a hand clap, an activation pattern and low-voltage fast discharge appear abruptly in association with alertness of behaviour. This alteration is termed the EEG. arousal reaction and provides an objective record of the rôle of afferent stimulation in evoking the waking state and of the characteristic maintenance beyond the period of the stimulus. Magoun's experiments demonstrated that direct electrical stimulation of the brain-stem was capable of reproducing the electro-cortical events encountered in awakening from sleep or in the EEG. arousal reaction. The experiment showed that this could only occur by the ascending transmission of an activating influence through the medial reticular formation, since other sensory pathways had been blocked. Destruction of the rostral portion of the central reticular formation, as already stated above, leads to somnolence. French, Verzeano and Magoun (1953) have studied the effect of anaesthetics upon the central reticular formation and state that they block this pathway at a time when conduction in the lateral afferent paths is unaffected. They believe that blockage of the central reticular formation in this way is the main factor in anaesthesia, though some blocking of the lateral system may occur and some change in the interneuronal cortical systems.

Thus, there is some evidence that the central reticular formation is concerned with the maintenance of the whole cerebral cortex in a state which favours attention and wakefulness, that the depression of its activity leads to sleep or other states of

unconsciousness and that its stimulation plays an important part in the waking process. It is likely that sensory stimuli when they awaken a subject do so chiefly through their influence upon the central reticular formation rather than through the afferent pathways concerned in conscious sensation.

Stupor and Coma

In the past the term hypersomnia has been used to describe a state in which the patient has been thought to be pathologically sleepy, the resemblance to sleep lying in the fact that he can be to some extent aroused by the kind of stimuli which arouse a healthy person from sleep. This condition was frequently seen during the epidemic of encephalitis lethargica and was responsible for its popular name of "sleepy sickness". It has been recognized, however, that the mental state of such patients when aroused, unlike that of persons awakened from normal sleep, is far from normal, which led Jefferson to propose the term *parasomnia* for this condition. Until we know how far such a patient is in a state physiologically similar to that of normal sleep it is probably better to avoid any term which suggests an identification which may be misleading, and to speak of stupor instead of *parasomnia* or hypersomnia. We may then distinguish broadly two different states of unconsciousness, coma and stupor. In coma the patient cannot be aroused by any stimulus however vigorous and if any response is elicitable at all it is merely of a reflex nature and does not indicate the presence of any degree of consciousness. The stuporose patient, on the other hand, can be aroused in the sense that, when sufficiently vigorously stimulated, he responds by behaviour which appears to indicate awareness of his surroundings. Between coma and complete consciousness there are many degrees and modifications of consciousness, and it has already been possible to distinguish clinically several varieties of stupor, one of which, *akinetic mutism*, has been described above. Careful observation is likely to add to these. No distinction between sleep and waking can be observed in the comatose patient. In the stuporose patient not only may some form of awakening occur in response to stimuli, but in the certain states of stupor spontaneous changes between the sleeping and waking state may occur. French (1952) reviewing the functions of the central reticular formation of the brain stem in relation to consciousness wisely points out that "these data suggest the inadvisability of considering the reticular activating system as a 'centre of consciousness' or a 'centre of wakefulness',

in that afferent impulses are required to excite it and the manifestations of its activity are expressed only through its influence on other subcortical structures and on the entire cortex. In the absence of such higher centres this system would appear to have no more intrinsic function than has the lateral geniculate nucleus without the visual receptive area of the cortex. The area would seem to serve, therefore, as a complex relay system energizing in some way normal activity of more highly developed centres, the integrative function of which is essential to the adaptive behaviour of the waking human being."

Hallucinations

The term hallucination is by no means easy to define. Henderson and Gillespie (1944) say that "hallucinations are mental impressions of sensory vividness occurring without external stimulus. They are distinguished from illusions, which are similar impressions depending, however, on a misinterpretation of an external stimulus." This definition of hallucinations, however, would include the teichopsia of an attack of migraine and the dysæsthesiæ which form the content of an attack of sensory epilepsy, yet neither of these is commonly termed a hallucination. A true hallucination, in addition to the features mentioned, must possess the perceptual characteristic of externality, that is to say though it occurs without an external stimulus it appears to come from outside. It is not relevant to the definition of a hallucination whether the patient does, or does not, believe in the reality of its external source: a patient's insight into this question may change in relation to the same hallucination in the course of time. Although an illusion is defined as a misinterpretation of an external stimulus, illusions in some circumstances are closely related to hallucinations and may occur as symptoms of hallucinatory states.

The principal circumstances in which hallucinations may arise are as follows. (1) In dreaming and the hypnagogic state, (2) in pathological disturbances of sleep, (3) as a result of organic disease of the sense organs or central nervous system, (4) in states of intoxication, particularly after the administration of certain drugs, and (5) in certain psychoses. It is through the study of hallucinations produced by organic disease of the sense organs and nervous system, and by the administration of drugs, that we are likely to learn most about their nature and, in particular, about the significance of their occurrence in the psychoses.

A recent study by Lhermitte (1951) gives a comprehensive review of hallucinations with particular reference to those resulting from nervous disease. The relationship between a hallucination occurring in the sphere of one sensory modality, and a lesion of the anatomical structures concerned, is clearly a very complex one, since, as Lhermitte points out, visual hallucinations may occur in patients suffering from severe visual loss as the result of disease of the eyes, or with lesions in any part of the visual pathways as well as elsewhere in the nervous system. When a hemianopia is present the hallucinations may be seen in the normal half-fields or in the blind half-fields. Lhermitte himself has described what he terms the peduncular hallucinosis, which is the occurrence of hallucinations, especially visual hallucinations, as a result of lesions of the upper part of the brain-stem. Lhermitte interprets these hallucinations as the expression of a dissociation of the state of sleep in which, although bodily activity remains awake, the mind is plunged into a special condition which permits the appearance of images analogous to those which normally occur only in dreams. This view receives support from the evidence described earlier in this chapter which suggests that this part of the brain plays an important rôle in the regulation of states of consciousness and unconsciousness. Hallucinatory states produced by drugs are remarkable for the diversity and richness of their sensory characteristics. The best known hallucinogenic drug is mescaline, but recently in the course of researches into the pharmacology of ergot derivatives, one of these, a compound of lysergic acid, was accidentally found to have hallucinogenic properties. The effect of mescaline has been studied by many observers (see Guttman (1936) and Marshall (1937)). The hallucinations may involve any of the senses, but the visual disturbances are undoubtedly the most striking, consisting of geometrical forms, ornaments, architectural patterns, carpets or lattice work arranged in long rows or some other regular manner, often brilliantly coloured and constantly changing. Distortion of objects seen is frequently experienced and alteration in the perception of movements may occur. Mescaline hallucinations sometimes consist of elaborate and fantastic scenes. One striking feature is the occurrence of synæsthesiæ, that is, the irradiation of sensation from one sense to another, for example, colours may be evoked and modified by listening to music. Equally bizarre are the experiences of distortion of the body-image. Appreciation of time may be disordered: usually time seems to move very slowly; seconds seem minutes; minutes seem hours. It

may even appear to stand still. Perhaps it is not surprising that in such circumstances awareness of the personality and of objects of reality themselves become disordered, so that the subject complains of depersonalization, or splitting of the personality, and of derealization, or a sense of unreality in the objective world.

Studies are now being made into the effects of lysergic acid (Stoll, 1947, Bradley, Elkes and Elkes, 1953). This drug can produce hallucinations in minute doses, for example, 15 to 60 micrograms in an adult. Bradley, Elkes and Elkes state that the characteristic disturbances are depersonalization, heightened awareness, and fluctuating, incongruous affect. Eight subjects experienced visual symptoms and seven distortion of body image.

So far we have been considering the production of hallucinations by drugs, but this seems the most convenient place to discuss those which can be caused by another physical agent, even in normal individuals, namely, by exposing them with the eyes closed to a flickering light (Walter, 1953). This experience is most marked when the flicker is between 8 and 25 flashes per second and takes a variety of forms. Usually, says Grey Walter, it is a sort of pulsating check and mosaic, often in bright colours. At certain frequencies, around ten seconds, some subjects see whirling spirals, whirlpools, explosions or catherine wheels. Other abnormal sensations are described, such as feelings of swaying, jumping or swimming. There may be organized hallucinations, that is, complete scenes, as in dreams, involving more than one sense. All sorts of emotion are experienced; fatigue, confusion, fear, disgust, anger, pleasure. Sometimes the sense of time is lost or disturbed: one subject said that he had been "pushed sideways in time;—yesterday was at one side, instead of behind, and tomorrow was off the port bow."

In the combination of hallucinogenic drugs, visual flicker and electro-encephalography, we have new techniques of investigation of hallucinatory states which can be applied both to animals and to human subjects and are of great promise. Already Bradley, Elkes and Elkes have applied this combination of techniques to the investigation of human volunteers who took lysergic acid and Bradley and Elkes (1953) have studied the effect of this drug or the electrical activity of the brain of the conscious cat.

Thus, to sum up, it appears that (1) when hallucinations occur in association with organic lesions of the sense organs or central nervous system they cannot be explained solely as the result of such lesions, but any explanation must also take into account the mental state of the patient as a whole. (2) Dreams may be regarded

as normal hallucinations and hypnagogic hallucinations may also be normal in the sense that they occur in a transitional phase between waking and normal sleep. (3) The peduncular hallucinosis may be regarded as a disturbed state of consciousness resulting from a disorder of the physiological basis of consciousness. (4) The mode of action of the hallucinogenic drugs has yet to be determined and it is likely that they will throw further light upon the physiological basis of consciousness and also its disorder in the psychoses. (5) The study of the psychological effects of visual flicker and their electro-encephalographic correlates may also throw light on the same question.

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CHAPTER 6

THE CEREBELLUM AND ITS DISORDERS

DURING recent years the technical advances of anatomy and physiology have been applied to the study of the cerebellum and its connections with a resulting enlargement of our knowledge which has recently been reviewed comprehensively from the anatomical standpoint (Jansen and Brodal, 1954).

Comparative Anatomy

Jansen (1954) accepts the view advocated by Larsell that the mammalian cerebellum comprises two fundamental subdivisions, the corpus cerebelli and the flocculo-nodular lobe. The corpus cerebelli is divided by the fissura prima into the anterior and posterior lobes. The anterior lobe may be further subdivided into three or five sublobules, while the posterior lobe is divisible into five lobules, namely, the lobulus simplex, the ansiform lobule, the paramedian lobule, the paraflocculus dorsalis and the paraflocculus ventralis. In Jansen's view the subdivision of the cerebellum in a series of transverse rostro-caudally arranged lobes and lobuli does not warrant the abolition of the classical subdivision of the mammalian cerebellum into vermis and hemispheres. The fundamental structural plan of the mammalian cerebellum is a combination of a transverse and a sagittal system of subdivisions.

Afferent Cerebellar Connections

Brodal (1954) reviews the afferent cerebellar connections.

(1) **The Dorsal Spino-cerebellar Tract.** It is generally agreed that the dorsal spino-cerebellar tract originates in the cells of Clark's column. Coming into the cerebellum through the restiform body the fibres fan out to reach their destination. The bulk of the dorsal spino-cerebellar fibres terminate in the vermis of the anterior lobe.

(2) **The Ventral Spino-cerebellar Tract.** The ventral spino-cerebellar tract has an uncertain origin in the grey matter of the spinal cord. Most fibres seem to cross to the other side immediately after their origin, the crossing being completed in the

course of a few segments. It ascends to the pons where it turns to enter the cerebellum via the brachium conjunctivum to be distributed to the anterior lobe.

(3) Fibres also reach the cerebellum from the external cuneate nucleus.

(4) **Olivo-cerebellar Connections.** It has long been known that the inferior olive sends fibres to the cerebellum via the opposite restiform body. Brodal states that while all parts of the vermis receive fibres from the accessory olives, the origin of fibres to the cerebellar hemispheres is the principal olive. The olivo-cerebellar fibres end as mossy fibres. The spino-olivo-cerebellar projection system shows a close similarity to the dorsal spino-cerebellar tract.

(5) **Ponto-cerebellar Connections.** In man and the higher mammals the ponto-cerebellar connections are the most important of all afferent cerebellar pathways. Brodal believes that the entire cerebellar cortex, probably with the exception of the flocculo-nodular lobe and the lingula, receives pontine fibres and that the areas projecting on to the vermis are largely different from those projecting on to the hemispheres. In this connection the cortico-pontine projection is of interest. In the macaque it is predominantly, but not exclusively, ipsilateral and fibres come from all four lobes of the cerebrum. Brodal states that each of the four lobes projects chiefly on its particular longitudinal zone in the pons which suggests that the cerebellar vermis will be influenced chiefly from the frontal and temporal lobes, but the frontal lobes may in addition act on the hemispheres.

(6) **Reticulo-cerebellar Connections.** In view of recent discoveries of the importance of the central reticular formation it is of interest that connections between this and the cerebellum have been established.

(7) **Vestibulo-cerebellar Fibres.** These are of special importance and consist of direct fibres running from the vestibular root and secondary fibres derived from the vestibular nuclei. Both are related first and foremost to the flocculo-nodular lobe.

Other fibres reach the cerebellum from the red nucleus, the tectum of the mid-brain and the trigeminal nerve and its nuclei.

Efferent Connections

According to Jansen (1954) the efferent connections of the cerebellum fall into three parts. (1) The fibres connecting the

cortex of the cerebellum with the cerebellar nuclei, (2) the cerebellar nuclei themselves and (3) the outgoing pathways from the cerebellar nuclei. All fibres leaving the cerebellar cortex are formed by Purkinje cells. Short fibres connect all parts of the cerebellar cortex with the nuclei: long fibres which pass beyond the nuclei are derived preponderantly from the cortex of the vermis and the flocculus. These pass through the inferior cerebellar peduncle and terminate in the vestibular nuclei.

The cerebellar nuclei are closely associated with the vestibular nuclei and in all mammals, except monotremes, consist of a nucleus medialis, a nucleus interpositus and a nucleus lateralis. The nucleus medialis is held to be homologous with the nucleus fastigii, the nucleus interpositus with the globose and emboliform nuclei, and the nucleus lateralis with the nucleus dentatus in man.

The main connections of the efferent fibres from the cerebellar nuclei are with the vestibular nuclei, the reticular formation of the brain-stem, the motor nuclei of the 5th and 7th cranial nerves, the red nucleus and the ventral thalamic nucleus.

The Structural Organization of the Cerebellum in Relation to Function

Brodal and Jansen (1954) review the present state of our knowledge of cerebellar morphology and morphogenesis in relation to cerebellar function and localization.

The Flocculo-nodular Lobe. The flocculo-nodular lobe is phylogenetically ancient and its connections are chiefly with the vestibular apparatus. It also receives afferent fibres from the inferior olive. The effects of isolated removal of the nodulus in animals, including monkeys and chimpanzees, have been studied by Dow (1938). These consist of a disturbed equilibrium manifesting itself in unsteadiness on standing and walking, but the other symptoms associated with the removal of the entire cerebellum are absent. Dow interprets these symptoms as primarily due to vestibular dysfunction and he draws attention to the similarity of the symptoms of removal of the nodulus to those occurring in cases of medulloblastoma of the posterior vermis in man—a tumour probably arising from the nodulus. Bard and his collaborators (Bard *et al.*, 1947) have shown that localized removal of the nodulus in dogs confers protection from motion-sickness.

The Anterior Lobe. The problem of functional localization in the anterior lobe is discussed by Brodal and Jansen and also by

Fulton (1949). Brodal and Jansen believe that many questions must remain unanswered. It appears to be established, however, that physiological studies agree with the anatomical data which distinguish three longitudinal zones within the anterior lobe. It is at present difficult to assess the conflicting results obtained in electrophysiological studies of the cerebro-cerebellar relationship. Direct stimulation may produce either inhibitory or facilitatory effects. The difficult and complicated question of somatotopical representation in the anterior lobe is fully discussed by Brodal and Jansen in the light of modern electrophysiological studies and ablation experiments.

The Cerebellar Cortex. Most afferent cerebellar connections terminate in the cerebellar cortex which is also the starting point for the main outgoing pathways. There is experimental evidence that most of the afferent fibres terminate as mossy fibres. Evidently the cerebellar cortex must co-ordinate the afferent impulses and regulate their effect upon the efferent fibres, but Brodal and Jansen state that it is at present scarcely possible to envisage how the cerebellar cortex works.

Cerebellar Localization

Reviewing the question of cerebellar localization in the light of present knowledge Brodal and Jansen state that the concept of a functional localization, according to which three principal areas are distinguished, is supported by recent evidence. The flocculonodular lobe is related to the vestibular apparatus. The spinal part of the cerebellum comprises the pyramis and uvula, the vermis and the intermediate part of the anterior lobe. The three longitudinal zones of the anterior lobe, the vermis, intermediate part and lateral part are not equivalent. The third part is the remainder of the corpus cerebelli.

The somatotopical localization demonstrated by physiological methods in the anterior lobe and the paramedian lobules cannot be explained on an anatomical basis as yet, and in the other cerebellar lobules there is so far no anatomical evidence for a somatotopical localization. The authors stress the diffuse borders of the "functional" areas as contrasted with the morphologically distinguished subdivisions: even the primary cerebellar fissures do not form entirely reliable landmarks of functionally different cerebellar areas. It appears that "the cerebellum normally always functions more or less as a whole". It is doubtful if the terms

palaeocerebellum and neocerebellum, based on gross morphology, can be satisfactorily defined in terms of function.

Cerebellar Hypotonia

Fulton (1949) discusses cerebellar hypotonia in the light of animal experiments. He agrees that hypotonia does not follow removal of the cerebellum from cats or dogs provided that the underlying vestibular nuclei are not injured, but his own work with Botterell shows that hypotonia occurs in monkeys and baboons following lesions restricted to the neocerebellum, and in the chimpanzee a neocerebellar lesion is followed by conspicuous hypotonia. These animals after operation were so loose-jointed on the affected side that they would hit their own faces when a resisting arm was suddenly released, and their knee jerks were pendular as in man following gunshot wounds of the cerebellum. Fulton concludes that cerebellar hypotonia only occurs after lesions of the more highly organized cerebellum. He observed the same motor disturbances after removal of the neocerebellum in monkeys and chimpanzees as were described many years ago by Holmes in man. He emphasizes that there is no disturbance of equilibration after neocerebellar lesions: the effect is limited to the sphere of volitional movement.

The Role of the Muscle Spindles

Recent physiological work on the muscle spindles promises to be of great importance for our understanding of muscle tone. Recent work on this subject has been summarized by Kuffler and Hunt (1952) and by Eldred, Granit and Merton (1953). A muscle spindle consists of two contractile muscular poles (the intrafusal muscles) joined by a non-contractile sensory portion. It is believed that the rate of discharge of the end-organ is determined only by the extension of this sensory portion. The muscle spindle lies among the main muscle fibres parallel to them, and as it shares their attachment its length will vary with theirs. If the intrafusal muscle bundle does not contract, the single sensory endings record the length of the main muscle fibres. It has been shown that the intrafusal muscle bundle receives its motor supply through small fibre efferents, the γ efferents of the anterior roots. These fibres, by making the muscular poles contract, extend the sensory portion of the muscle spindle and increase the frequency of its discharge, which, on the other hand, is diminished by muscle shortening and by active contractions. Thus, as Eldred, Granit

and Merton point out, when the γ system is active the spindle signals the difference between muscle shortening and intrafusal fibre shortening.

These authors have studied the general effect of γ activity indirectly through its influence on the sensory discharge in a single afferent isolated in a dorsal root filament. They have used the information thus obtained to investigate the supraspinal control of the muscle spindles. They found that in decerebrate cats the influence of the γ fibres was evident at all tensions. Deafferentation did not usually significantly diminish this activity, but deafferentation led to a sudden drop. Investigating the effect of supraspinal control Eldred, Granit and Merton found that γ activity was inhibited by stimulation of a spot in the opposite internal capsule and excited by a spot in the opposite inferior colliculus.

Investigating the tonic neck reflexes Eldred, Granit and Merton found that movements of the neck which diminished muscle tone were associated with inhibition of the γ activity, while, on the other hand, movements which increased muscle tone caused a great increase of γ activity. After deafferentation the same experiment had the same effects on γ activity, but there was no longer any activity in the alpha moto-neurons.

Thus it would seem that the physiology of muscle tone is much more complex than used to be thought. Higher centres influence discharges in the γ fibres which regulate the contraction of the muscle spindles and hence the afferent impulses derived from them. These, in turn, exert their influence upon the alpha moto-neurons and hence upon the muscle fibres.

The Spino-Cerebellar Degenerations

Greenfield (1954) has recently published a monograph on the spino-cerebellar degenerations. He classifies them as follows:

A. *Predominantly Spinal Forms.*

1. Friedreich's Ataxia.

Association with neural amyotrophy of Charcot, Marie and Tooth.

Hereditary areflexic dystasia of Roussy and Levy.
Familial claw-foot with absent tendon jerks. (Symonds and Shaw).

Posterior column ataxia (Biemond).

2. Hereditary Spastic Ataxia.
(Certain families of Marie's hereditary ataxia, Sanger-Brown, Klippel-Durante).
Association with hereditary spastic paraplegia.

B. Spino-cerebellar Forms.

1. Menzel Type of Hereditary Ataxia.
2. Subacute spino-cerebellar degeneration (Carcinogenic and sporadic).

C. Predominantly Cerebellar Forms.

1. Holmes's Type of Hereditary Ataxia.
(Late cortical cerebellar atrophy (Marie, Foix and Alajouanine).
Subacute familial type (Akelaïtis).⁻
2. Diffuse atrophy of Purkinje cells. (Toxic and carcinogenic.)
3. Olive-ponto-cerebellar atrophy (Dejerine, André-Thomas).
4. Dentato-rubral atrophy.
"Dyssynergia cerebellaris myoclonica" (Ramsay Hunt).

Friedreich's Ataxia. Greenfield reviews the pathological and clinical features of Friedreich's ataxia and discusses the significance of its association with heart disease. Abnormal electrocardiograms are fairly common including the changes associated with heart-block. Russell (1946) has reported interstitial myocarditis. Greenfield concludes that the evidence of these examinations agrees with that obtained by the electrocardiogram in suggesting a progressive degeneration of the heart muscle, until eventually heart failure sets in, or a slight fever or minor illness causes serious decompensation and death. On the subject of the association of Friedreich's ataxia with atrophy of the Charcot-Marie-Tooth type Greenfield says that this is not surprising in view of the similarity in the pathology of the two diseases. The number of recorded cases, however, remains quite small. Roth (1948) has drawn attention to it.

Greenfield considers that it is difficult to demarcate these cases from the rather mild familial condition described by Roussy and Levy in 1936 and later named by them "hereditary areflexic dystasia". This condition is characterized by pes cavus and

absence of deep reflexes in the legs and diminution or absence of those in the upper limbs. In some cases there is also wasting of the legs below the knees or spreading to involve the lower third of the thigh. The small muscles of the hands are often affected, producing the typical claw hand. These signs relate the condition to peroneal atrophy. On the other hand unsteadiness of gait, clumsiness of the hands, nystagmus and extensor plantar responses bring the condition into line with Friedreich's ataxia.

Hereditary Cerebellar Ataxia. Greenfield reviews the history of hereditary cerebellar ataxia and concludes that the reported cases fall into two main groups. Type A, the Menzel type, is characterized by atrophy involving the middle cerebellar peduncle, the nuclei pontis, the medullary olives, the cerebellar white matter and the cortex in that order of constancy. One or more of the long tracts of the spinal cord, i.e. the dorsal columns, the direct and indirect spino-cerebellar tracts and the pyramidal tracts, are degenerated in most of the recorded cases. In some families the cranial motor nerves, especially the ocular motor and hypoglossal nerves, and the anterior horn cells are also atrophied. In this form of the disease the newer parts of the cerebellum phylogenetically and those which mature latest in individuals are usually most involved; the degeneration is greatest in the hemispheres, with relative or complete sparing of the vermis. This group falls into the general category of olivo-ponto-cerebellar atrophy.

In type B, the Holmes type, the degeneration is greatest in the cortex of the superior half of the cerebellum, especially the vermis, and those parts of the inferior olives which are related anatomically to the degenerated areas of the cerebellar cortex. In some families the dentate nucleus and superior cerebellar peduncle have also undergone degeneration. In type A, therefore, the disease is of the cerebellopetal type, but in type B of the cerebellofugal type, and in the latter the palæo-cerebellum is usually most severely affected. Greenfield points out that it is a commonplace that no differential diagnosis is possible during life between the different forms of cerebellar and spino-cerebellar disease. Apart from the tendency for the disease in type B to begin later, to last rather longer and to be associated with some mental enfeeblement during the later stages there do not appear to be any clinical symptoms or signs by which this type can be distinguished from type A. It has been pointed out, however, that Parkinsonism is much more common in cases of olivo-ponto-cerebellar atrophy than in other forms of cerebellar degeneration.

Late Cortical Cerebellar Atrophy. Discussing the claim of Marie, Foix and Alajouanine to have isolated a form of cerebellar degeneration coming on in later life, a clinico-pathological entity in which atrophic changes were found especially in the palæo-cerebellum, Greenfield concludes that it is difficult to find any salient differences between their cases and those of Holmes. The distribution of the atrophy both in the cerebellum and olives was almost identical and in other respects also the two descriptions are remarkably similar.

Subacute Cerebellar Degeneration. This syndrome is discussed elsewhere (see pp. 155, 156).

Olivo-ponto-cerebellar Atrophy. This name was given by Dejerine and Thomas to a form of disease of the cerebellum and brain-stem coming on at a later age and showing in the majority of cases no evidence of familial incidence or hereditary transmission. In a typical case the diagnosis may be made pathologically on naked-eye inspection of the brain owing to the great shrinkage of the ventral half of the pons and the disappearance of the olivary prominences on the surface of the medulla. The cerebellum is greatly reduced in size and may not show the severe cortical sclerosis which is seen in a more purely cortical type of cerebellar degeneration. Histological examination shows great loss of cells in the nuclei pontis which may be completely replaced by neuroglial cells and fibres. The olives also lose most or all of their fibres and are heavily sclerosed.

The clinical picture described by Dejerine and Thomas included weakness and unsteadiness of the legs with affection of the speech and clumsiness of the hands. Their patients also suffered from incontinence of urine. Later studies have added to this clinical picture rigidity of the Parkinsonian type in a large proportion of cases, with tremor in some. Greenfield accepts the view that there is a correlation between the symptoms of Parkinsonism and lesions of the substantia nigra. Choreiform movements have been observed only in patients in whom the symptoms came on during the second and third decades. The tendency for a mild or more severe degree of dēmentia to appear during the later stages of the disease appears to be rather less in olivo-ponto-cerebellar atrophy than in cerebello-olivary degeneration or Friedreich's ataxia, but Greenfield considers that it is too definite to be accounted for solely on the basis of senility.

Dentato-rubral Atrophy (the Ramsay Hunt syndrome). This is a condition originally described by Ramsay Hunt in which

myoclonus epilepsy is associated with progressive symptoms of cerebellar ataxia. This is a rare condition. It has been suggested that the myoclonus is associated with atrophy of the dentate nuclei, but Greenfield considers that severe rhythmic myoclonus, brought on by proprioceptive stimuli and associated with epilepsy, may be connected with extensive loss of Purkinje cells without any lesion in the nucleus dentatus.

Blindness in Hereditary Ataxia. Greenfield reviews the incidence of blindness in hereditary ataxia. This may be due to (1) retrobulbar neuritis, which is very rare, (2) optic atrophy of rapid onset with a reduction of the visual fields and (3) slow diminution of visual acuity with concentric narrowing of the visual fields. Ophthalmoscopically there may be pallor of the whole disc or the temporal half which may be combined with pigimentary retinal degeneration.

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CHAPTER 7

POLIOMYELITIS AND COXSACKIE DISEASE

POLIOMYELITIS

THE chief recent advances in our knowledge of poliomyelitis have been concerned with the causative virus, which can now be grown on tissue cultures, the epidemiology of the disease, the clearer recognition of some of its clinical manifestations, and the treatment, particularly of respiratory and bulbar paralysis.

The Poliomyelitis Virus

A valuable review of the present state of our knowledge of the bacteriology and epidemiology of poliomyelitis has been published by the World Health Organization (Technical Report series 81, 1954). Three immunological types of human poliomyelitis virus have now been identified. These are known as "Brunhilde" (type 1), "Lansing" (type 2), and "Leon" (type 3). These strains are now identifiable by virus neutralization tests with specific antisera. Observations show that outbreaks of epidemic proportions are attributable mainly to type 1 strains. However, epidemics apparently caused by type 3 strains have recently been described. Type 2 strains are known to be widely disseminated, but have usually been detected in sporadic cases. The size and morphology of poliomyelitis virus have been studied by electron micrography and other methods. The particle size has been estimated to be 10 to 30m μ , the poliomyelitis virus thus being one of the smallest of the viruses. It is highly resistant to chemical agents, but sensitive to heat and to desiccation. Application of heat is therefore probably the most practical means of disinfection of materials containing poliomyelitis virus. The treatment of stools with chloride of lime in a concentration sufficient to destroy typhoid bacilli does not destroy the virus.

Epidemiology

There are still many unsolved problems in the epidemiology of poliomyelitis. Earlier experimental work showed that monkeys could be readily infected by the olfactory route and this led to

the supposition that the infection was spread mainly by inhalation of droplets into the nose. Now, however, it is believed that the portal of entry is the mouth and that the primary site of infection is the pharynx and the rest of the alimentary tract. The virus is mostly readily found in the oropharynx for three to five days before and for three to seven days, or rarely as long as eleven days, after the onset of illness. It has been recovered from the stools as long as three weeks before the onset of symptoms. During the first ten to fourteen days after onset practically every patient excretes virus in the stool. By three weeks after the onset approximately half the patients no longer excrete virus, and by five to six weeks after the onset only 25 per cent of the patients still excrete the virus. In a small percentage excretion may continue for twelve weeks.

It is not yet certain how the virus spreads from the alimentary tract to the central nervous system. Experimental work has demonstrated that it can pass readily along nerve fibres and it has been thought that it reaches the nervous system by the autonomic nerves from the alimentary canal. Recently, however, the virus has been shown to be present in the blood stream in monkeys and chimpanzees experimentally infected and it is known that viraemia may also occur in man, so that the blood stream offers an alternative route. Since, however, it has been shown that there is a high incidence of bulbar poliomyelitis after tonsillectomy, it is probable that in such cases the virus spreads to the brain-stem by nervous pathways. Dental extractions have also been thought to precipitate an attack, and so also may trauma to a limb, including inoculation.

The distribution of the disease in the various age-groups is a valuable indication of immunity. In those countries in which infection is highly prevalent the occurrence of cases is usually limited to the lowest age groups, which suggests that the older members of the population have acquired an effective resistance. In temperate climates, and where hygienic conditions are generally good, immunity is apparently acquired later and is less solid. Consequently poliomyelitis is increasingly common in persons of older age in such areas.

Serological data indicate that immunity to all three types of virus is generally acquired by natural exposure, but immunity to one type of virus does not protect against the other two. There is some doubt whether a lasting immunity is acquired from a single infection, or whether it depends upon repeated exposure.

The fact that the level of antibodies after infection tends to decline with the passage of time suggests that the high levels of later life are developed by reinforcements from multiple infections.

All the evidence suggests that poliomyelitis virus is spread by means of the transfer of pharyngeal and intestinal excretions of infected human individuals. In an infected family most members appear to become infected at the same time, though multiple paralytic cases occur in the same family in less than 10 per cent of infected families. It is stated that for every person with symptoms there may be 10 to 100 infected individuals with no obvious illness. Sewage contains large amounts of virus when infection occurs in a community and polluted water may convey the infection when used for bathing, washing or watering fruit or vegetables. Though flies can readily become contaminated there is little evidence that they play an important part in the spread of the disease.

Poliomyelitis is a world-wide infection. Widespread epidemics have occurred for many years in the U.S.A. A serious epidemic occurred in Great Britain in 1947 and further epidemics have occurred in 1949, 1950 and 1952. In 1952 Denmark, Germany and Belgium also suffered seriously. In both northern and southern temperate climates the disease is more prevalent in summer than in winter, whereas in tropical areas the cases occur more uniformly throughout the year, but how climate operates is unknown. In general, where living conditions and hygiene are bad, and the population is crowded together, poliomyelitis occurs at an earlier age than where the reverse is the case. The incubation period ranges from three days to five weeks between exposure to infection and the onset of the "major" illness.

Clinical Characteristics

The main clinical characteristics of poliomyelitis have, of course, been well-recognized for many years. Nevertheless recent observations have in some instances brought fresh details to light, while the change in the behaviour of the disease has directed more attention to the clinical features of bulbar and respiratory paralysis. It is necessary, therefore, to review certain aspects of the clinical picture of poliomyelitis which are of special importance in relation to epidemiology and treatment. These will be found more fully discussed in the report of the World Health Organization, mentioned above, and in Ritchie Russell's book "Poliomyelitis" (1952).

It has long been recognized by epidemiologists that paralysis is a rare manifestation of infection with the poliomyelitis virus. It is important, however, that this fact should be known as widely as possible, since it is of far more than academic importance, because patients who suffer from non-paralytic forms of the disease appear to be at least as likely to spread the infection as those with actual paralysis. As the report of the World Health Organization states, "it must be strongly emphasized that paralysis is an infrequent complication of poliomyelitis infection in man, and that most persons who become infected either show no symptoms or else develop a transient abortive or 'minor' illness." The following classification of the varieties of illness in poliomyelitis is now generally recognized.

(1) **Inapparent Infection.** Persons who come in contact with patients suffering from poliomyelitis are frequently infected without showing any clinical evidence of this process, and this is probably the way in which part of an exposed population develops immunity. Such infections are known as inapparent, asymptomatic, or "silent", and can be recognized only in the laboratory by the recovery of virus or the demonstration of an increase of antibody in the blood serum.

(2) **Abortive Poliomyelitis.** The clinical manifestations of abortive poliomyelitis are merely those of a brief general acute infection characterized by such symptoms as fever, headache, sore throat, listlessness, anorexia, vomiting, constipation and pains in the muscles and abdomen. These illnesses are brief, lasting only from one to three days, and are more often encountered in children than in adults. Proof that such illnesses are due to poliomyelitis cannot be made without virological studies, but their true nature may be suspected when they occur in the course of an epidemic of poliomyelitis, and especially in persons who are known to have been associated with a sufferer from the disease.

(3) **Non-paralytic Poliomyelitis.** This is one form of what has come to be known as the "major" illness. The variety of ways in which the "minor" illness, the "major" illness and paralysis may be related to one another are illustrated in Fig. 3. In the "major" illness it is believed that the virus has reached the central nervous system, but this does not mean that it necessarily produces paralysis. Non-paralytic poliomyelitis is the term applied to the "major" illness in which definite manifestations of involvement of the central nervous system are added to those of the "minor" illness, but paralysis does not occur. The clinical features include

fever, headache, vomiting, pains in the back, neck, trunk or limbs, paræsthesiæ and stiffness of the back or neck. There is usually an increase of cells and protein in the cerebrospinal fluid.

The non-paralytic illness may clear up completely in the course

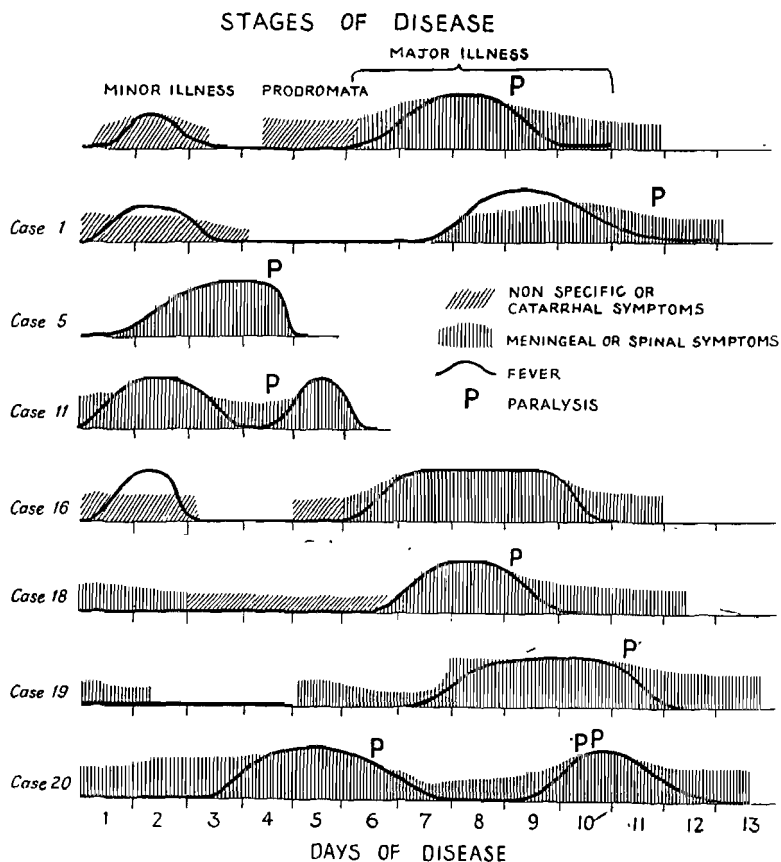


FIG. 3. Diagram to show various patterns which the disease may take, and the terms used to describe the stages of the disease. (Reproduced by kind permission from Ritchie Russell: Polio-myelitis. Edward Arnold & Co. Ltd.)

of from four to seven days, or may become more severe with the development of paralysis.

(4) **Paralytic Poliomyelitis.** Paralytic poliomyelitis usually develops after one to four days of a non-paralytic illness as described above. This period is therefore sometimes referred to as

"the pre-paralytic phase". Less commonly paralysis may be almost the first manifestation. In many cases the parâlysis involves only muscles innervated by the spinal cord, the so-called spinal paralytic form. Pain in the muscles often becomes more prominent as the paralysis develops. The paralysis is of the flaccid or lower motor neurone type and is typically asymmetrical in distribution. The muscles most commonly affected, in order of frequency, are those of the lower limbs, upper limbs, back, thorax including the intercostals, and diaphragm. The possibility of respiratory paralysis renders it necessary to make frequent examinations of the movements of the chest wall and to assess the power of the diaphragm by watching the movements of the epigastrium on inspiration.

Retention of urine is common in poliomyelitis and may even occur in the non-paralytic case. Careful examination should therefore be made for distension of the bladder. The retention is always transitory.

Bulbar paralytic poliomyelitis may occur as the only manifestation of the disease or in association with, or subsequent to, spinal paralysis. The early signs of bulbar disturbances, as Russell (1952) points out, include an indistinct voice, choking and spluttering with drinks, and refusal to eat or drink (really due to fear of choking). A rattling sound on respiration is due to the presence of mucus in the pharynx and is strongly suggestive of pharyngeal paralysis. It is essential in such cases to make a careful examination of movements of the palate, pharynx and vocal cords. Paralysis of muscles of the face, tongue, jaw and eyes, with disturbance of conjugate lateral deviation, may also occur. In severe cases vomiting, respiratory irregularity and circulatory collapse may result from involvement of the vital centres.

Other Cerebral Manifestations. There is considerable histological evidence that the virus of poliomyelitis may involve higher levels of the brain, and in particular the hypothalamus. Consciousness, however, is usually unimpaired except in cases with severe damage to the brain-stem. Nevertheless, a state of considerable anxiety may occur, which may have an organic basis and not be merely the patient's natural psychological reaction to his condition. There may be insomnia, or sleep may be disturbed by nightmares. Hallucinatory states sometimes occur. Nystagmus is not uncommon.

The Cerebrospinal Fluid. The cerebrospinal fluid usually affords valuable confirmation of the clinical diagnosis. In both the

non-paralytic and the paralytic illness there is usually an increase in the cell count which may range from 10 cells to over 500 per cubic millimetre. In the early stages more than 50 per cent of these cells may be polymorphonuclear neutrophils. As the illness progresses, the cell count falls, lymphocytes predominate and the protein content, which is usually raised in the early stages, tends to rise still higher so that a figure of 200 to 300 milligrams per cent is not uncommon two or three weeks after the onset. It must be borne in mind, however, that the cerebrospinal fluid is occasionally normal in undoubted instances of the disease.

Diagnosis

As stated above, it is impossible to diagnose the abortive form, or the "minor" illness, without virological studies which are rarely available. On clinical grounds it is usually difficult, and often impossible, to distinguish the pre-paralytic stage from other infections characterized by the clinical picture of an acute or subacute meningitis with a mixed or predominantly lymphocytic cell count in the cerebrospinal fluid, which include such conditions as mumps, infectious mononucleosis, lymphocytic choriomeningitis, herpes zoster, leptospiral meningitis due to Weil's disease or canicola fever, various forms of virus encephalitis and even tuberculous meningitis. In some of the conditions mentioned it may be possible to demonstrate the appropriate antibodies in the blood serum. The onset of tuberculous meningitis is usually much more insidious than that of poliomyelitis and in the former condition a fall in the chloride and sugar content of the cerebrospinal fluid is likely to be found and the presence of tubercle bacilli is, of course, pathognomonic.

The spinal paralytic form of the disease does not usually give rise to diagnostic difficulty. Shoulder-girdle neuritis, however, may be confused with poliomyelitis. This is a disorder which attacks chiefly males in early adult life, but may occur in older persons. The muscles paralysed are usually, but not invariably, those of the shoulder-girdle, and particularly serratus magnus. They are usually affected on one side, but sometimes on both. The paralysis is usually preceded by quite severe pain, which may last for several days, and is occasionally accompanied by some cutaneous sensory loss. There is usually little, if any, systemic disturbance and the cerebrospinal fluid may be normal or may contain a small excess of lymphocytes. Acute infective polyneuritis may also give rise to confusion since it may cause

widespread flaccid paralysis, including paralysis of respiration, and develop subacutely with fever. Acute infective polyneuritis, however, involves the limbs symmetrically, often affecting the proximal muscles more than the distal. Moreover it may be accompanied by sensory loss, and, finally, the cerebrospinal fluid exhibits a massive rise of protein content without an excess of cells.

Bulbar paralysis of acute or subacute onset associated with a febrile illness and an excess of cells in the cerebrospinal fluid is a picture which is rarely simulated by any other disease. However, an acute demyelinating encephalitis may attack the brain-stem, in which case all the above-mentioned features may occur. Such a disease, however, usually attacks the white matter and therefore gives rise to signs of damage to the pyramidal tracts and may also cause sensory loss.

Treatment

The treatment of a patient suffering from, or suspected of suffering from, poliomyelitis may require a number of difficult decisions which should be made in the light of the principles involved. Moreover, though modern methods of treatment have proved of the greatest value in saving life they require to be based upon an accurate knowledge of the nature and extent of the damage to the nervous system.

In the first place it must be borne in mind that a minor febrile or catarrhal illness occurring in the course of an epidemic of poliomyelitis may be due to infection with that virus. There is evidence, reviewed by Russell, that physical activity after the onset of the "major" illness may be an important factor in determining the severity of the subsequent paralysis. Though the amount of exercise taken prior to the onset of the "major" illness bore no very definite relationship to the development of paralysis, nevertheless a patient suffering from a "minor" illness, which, it is thought, may possibly be poliomyelitis, should for the next ten days or so be protected from undue fatigue.

As soon as the "major" illness has been diagnosed the patient should be kept completely at rest in bed and a decision must then be made whether he shall be nursed at home or moved to hospital and, if so, to what hospital. The considerations which have to be weighed at this stage are that any unnecessary movement, and particularly a long journey in an ambulance, may be dangerous, and that the condition may subside without the

development of paralysis and with the requirement of no more treatment than rest. On the other hand, if the diagnosis is in doubt the patient should usually be under observation in hospital and if, later, either respiratory paralysis or bulbar paralysis should develop, treatment in hospital will be essential. In any case it will often prove impossible to provide even simple nursing and adequate supervision of bed rest at home. Most patients, therefore, where the diagnosis of preparalytic poliomyelitis has been made will be moved to hospital. The question of what hospital they shall be moved to involves considerations some of which are discussed below. The main relevant consideration is where the best facilities for treatment are available within a reasonable distance. This may be at the local hospital for infectious diseases, or at a special unit at a general hospital, or a neurological hospital or a hospital for children's diseases.

General Management. During the acute stage, whether paralysis is present or not, the patient should be kept completely at rest in bed, which means that he should not be allowed to do anything for himself. Mild sedatives are often useful, especially for children, and analgesics may also be required. Retention of urine will necessitate catheterization. Lumbar puncture should be carried out only if it is necessary for diagnostic purposes, principally to exclude some other condition which may call for different treatment. No form of chemotherapy is known to have any effect upon the course of poliomyelitis. Such treatment will therefore be required only to deal with respiratory complications (see below). Purgatives are theoretically contra-indicated in the acute stage and a few days' constipation need cause no anxiety. After that an enema should be used if necessary.

The Treatment of Bulbar Paralysis. The dangers of bulbar paralysis are threefold. First, and most important, since the patient is unable to swallow, fluids or secretions may accumulate in the pharynx and then be sucked back into the lungs with inspiration. Similarly, if vomiting occurs with the patient lying on his back, the vomit may be inhaled. Secondly, bilateral abductor paralysis of the vocal cords may call for tracheotomy; and lastly, as already stated, the infection may extend to the vital centres of the medulla, usually with fatal results. To combat the first danger proper posturing of the patient is essential. Russell recommends that patients should be nursed in the semi-prone position, being turned from one side to the other every few hours while the foot of the cot or bed should be raised to make an angle

of 15° with the horizontal. A tilt of 5 to 10° may sometimes be sufficient, provided that the patient can be nursed in the prone position. When nursing in the supine position is unavoidable a tilt of this amount is inadequate to provide drainage, and over 15° is required in the supine position to give the same tracheal drainage as 5° in the prone position. If the foot of a six-foot bed is raised 18 inches, the angle of tilt is 15° . A mechanical sucker is required to remove pharyngeal secretions and laryngoscopy or bronchoscopy to remove tracheal secretion may be necessary. Bulbar paralysis may persist for a number of days and the patient requires to be nursed by nurses with special experience of the difficulties. The experienced nurse becomes familiar with the change in the breath sounds when the airways become slightly obstructed by mucus and she can use a binaural stethoscope to listen over the larynx in such cases. Feeding should be carried out by an œsophageal catheter, preferably passed by the nose. Penicillin should be given as a prophylaxis against pneumonia.

The Treatment of Respiratory Paralysis. A patient with poliomyelitis suffering from respiratory paralysis needs treatment by some method of artificial respiration which may be required for weeks, or even for months. Such artificial respiration may be effected by means of negative pressure operating through some device which sucks the thoracic cage outwards, or by positive pressure which inflates the lung by raising the pressure within the trachea. For uncomplicated respiratory paralysis the negative pressure method is the more suitable. The cuirass type of respirator (Kelleher, Wilson, Russell and Stott, 1952) which applies negative pressure directly to the chest and abdomen, though of great value and convenience in certain cases, is not as efficient as the box type of respirator in respect of the ventilation produced. Some form of box respirator, therefore, which encloses the whole patient except for his head, is the most suitable for general purposes. The use of these respirators has been discussed by Bourdillon, Davies-Jones, Stott and Taylor (1950). It requires considerable skill and experience. The authors point out that while the dangers of respirator treatment may be appreciable, it is important to use the apparatus as soon as any signs of involvement of the respiratory motor neurones can be detected. The vital capacity of most people is about eight times their tidal air when at rest. Consequently a patient at rest will not show distress from failure of the respiratory muscles until a very large proportion of their power is lost. In determining the first onset of respiratory

weakness a rough estimate can be formed by ascertaining how many numbers the patient can count verbally in one expiration. If the apparatus is available, however, some form of spirometer is much more accurate. By means of early measurements of vital capacity it is possible to detect the first signs of respiratory involvement, and tidal air measurements are indicated as a rough guide to the correct setting of respirator pressures so as to avoid under- or over-ventilation. Under-ventilation is perhaps the more dangerous, and an oximeter may be of great value for the detection of this. The indications for, and the technique of, respirator treatment are also discussed by Russell (1952) and the nursing of patients with poliomyelitis by Wain (1945) and in a publication, "Nursing for the Poliomyelitis Patient" (1948).

The Treatment of Respiratory Paralysis Combined with Bulbar Paralysis. The combination of these two forms of paralysis constitutes an extremely difficult problem for treatment. If the patient is treated in a respirator for his respiratory paralysis, this introduces the danger that the suction created by the machine will aspirate pharyngeal secretions, possibly into the lungs. There are three possible solutions of this problem—to maintain postural drainage while the patient is in the respirator, or to combine respirator treatment with tracheotomy, or to treat the patient by a combination of tracheotomy and positive pressure artificial respiration such as was used successfully in the recent epidemic in Denmark (Lassen, 1953), and has recently been reported on favourably by Smith, Spalding and Russell (1954). In the Danish epidemic the positive pressure was supplied by a hand-operated pump, while Smith and his colleagues used a motor pump. The advantage of the positive pressure method is that the use of a cuffed intratracheal tube effectively blocks the trachea to the downward passage of the pharyngeal secretion, and so protects the lungs.

Whatever method is used for the treatment of respiratory or bulbar paralysis, or the two combined, a team of experienced doctors and nurses will be necessary. A doctor accustomed to the use of the bronchoscope will be required to remove accumulated secretion from the bronchi and so prevent pulmonary collapse. X-ray of the chest may be required. Prophylactic penicillin should be given or other antibiotics as may be necessary. Acute gastric dilatation is a serious complication, and when it occurs a stomach tube should be passed and an attempt made to empty the stomach by gastric suction.

Control Measures

The control of the spread of poliomyelitis raises many difficult questions. The basic condition is obviously the recognition and notification of as many infected persons as possible, and all cases in which the diagnosis can be made, both non-paralytic and paralytic, require to be notified to the public health authorities. The patient requires to be isolated, whether he is nursed at home or in hospital. There has been some discussion as to the kind of hospital treatment which is most suitable. There is no doubt that of recent years the behaviour of the poliomyelitis virus in respect of its infectivity has changed. For many years patients suffering from acute poliomyelitis were nursed in general wards with no special precautions and contact-spread of the disease was extremely rare. Recently small epidemics in hospitals have been reported, though it has not always been clear that they were due to spread from a patient suffering from the disease. It is argued that a hospital for infectious diseases is therefore the most suitable place in which to nurse patients suffering from poliomyelitis. Not all such hospitals, however, are at present equipped with the necessary apparatus, trained staff and ancillary services for the treatment of respiratory and bulbar paralysis and in some instances a special unit in a neurological hospital or in a general hospital, or in a hospital for children's diseases may be a more suitable place. In such hospitals appropriate methods of isolation must be adopted and the nurses, if they have been trained in the nursing of this disease, will have been instructed in the risks of spread of the infection. The usual measures for dealing with throat discharges, faeces and soiled articles should be carried out. A minimum period of isolation should be three weeks from the onset of the "major" illness if paralytic, or from the onset of symptoms in non-paralytic cases, and periods of longer isolation may sometimes be considered advisable. It should be remembered that patients who have had poliomyelitis may continue to excrete virus in the stool for a much longer period and it is probably inadvisable for them to return to contact with children in less than six weeks, or associate for from six to eight weeks from the onset of the disease with orthopaedic patients or others in swimming baths for rehabilitation or pleasure.

Measures Regarding Contacts. There is abundant evidence that when a case of poliomyelitis occurs other members of the household are probably already infected. Children with familial

or intimate exposure should be confined to their homes for twenty-one days, avoiding over-exertion. Adults should observe maximum hygienic precautions and refrain from association with children other than their own. They should not handle foodstuffs served outside the family. Day nurseries and nursery schools should be closed if a case occurs, all the children and their siblings being treated in the same manner as family associates.

An outbreak in a residential school should be considered in the light of all the local circumstances. Often there is only a single case; sometimes an initial case is followed by one or two others at intervals of a week or two. It has been maintained in the past that, when one or two cases of poliomyelitis occur in a residential school, substantially the same conditions obtain as in the case of a family outbreak, namely, most if not all the residents have already been infected and it has been concluded that there is no risk in allowing the school to remain open, provided it is as far as possible isolated from the rest of the community, while, on the other hand, the dispersal of a large number of potentially infectious individuals constitutes a threat to the wider community outside. It is difficult today, however, to give an unqualified assent to these views. Where a school consists of a large number of residential houses the infection may well be limited mainly to a single house and it is by no means certain that individuals remaining in the school are exposed to no further risk. There can be no doubt, however, that the dispersal of the school involves an added risk to the community. In the circumstances, therefore, when a single case occurs in a residential school it is probably best to attempt to deal with it by localized isolation, for example of a dormitory or a house, but when further cases occur it is usually impossible to prevent the closure of the school.

Measures Regarding the Community. When an epidemic of poliomyelitis occurs the public should be instructed in the probable modes of spread of the disease and advised to wash their hands frequently, especially after defæcation and before eating, and protect food from flies and thoroughly wash uncooked foods, such as fruit and vegetables. In the presence of a severe local epidemic it would be wise to delay opening the schools after the summer holidays, but normally schools need not be closed nor public gatherings forbidden. Swimming pools with adequately chlorinated water need not be closed, but should not be overcrowded. Unchlorinated pools should be closed and people should be discouraged from bathing in rivers which may be contaminated

with sewage. Operations on the nose, throat and mouth should as far as possible be avoided during an epidemic.

The Production of Specific Immunity. The ideal method of immunization against poliomyelitis would be by means of a vaccine. Encouraging work is going forward in this field, but no safe and reliable vaccine has yet been produced. Passive immunization has been carried out by means of gamma-globulin. Gamma-globulin has been shown to be effective in the prophylaxis of poliomyelitis in primates infected with the virus and it would appear that a low level of circulating antibody may be sufficient to afford protection. Against the background of these experimental observations, having regard to the protective effect of gamma-globulin in measles and infectious hepatitis, Hammon and his collaborators in the U.S.A. carried out in 1951 and 1952 a large scale trial of gamma-globulin as a prophylactic during times of epidemic prevalence (Hammon *et al.*, 1952). Gamma-globulin appears to afford protection against the paralytic disease over a period of five or six weeks, whereas no protection was demonstrated during the week immediately following the inoculation. However, it has been claimed that children who received gamma-globulin during the week prior to onset of illness developed a modified disease, and that paralysis was mitigated.

The results of the mass use of gamma-globulin carried out on a large scale in 1953 have recently been reported (Report of the National Advisory Committee for Evaluation of Gamma-globulin, 1954). It is pointed out that the injections were made as a public health measure and not on an experimental basis, and there were not adequate controls. The conclusion drawn was that with the preparations involved and in the dosages used, the administration of gamma-globulin to familial associates of patients with poliomyelitis had no significant influence on the severity of paralysis developing in subsequent cases; the proportion of non-paralytic poliomyelitis occurring in subsequent cases in which gamma-globulin was given before the onset; and the classic pattern of familial aggregation of cases in the country at large. The Committee on Poliomyelitis of the World Health Organization considers, however, that the administration of gamma-globulin, which is everywhere in short supply, is justifiable in certain circumstances, namely, if it is given to intimate associates of a patient, particularly those of the same household, or to patients in a hospital ward or children in a nursery following the recognition of a case. The use of gamma-globulin is also indicated for the protection of

individuals coming from an uninfected area into an infected home or institution or to otherwise unexposed groups into which the infected person is introduced. The newborn infants of mothers developing poliomyelitis might reasonably receive gamma-globulin and also patients requiring tonsillectomy during a poliomyelitis epidemic. In the present state of our knowledge the true value of gamma-globulin, and the best method of using it, must remain uncertain.

Inoculation and Poliomyelitis. It is an old observation that it sometimes happens that in a case of poliomyelitis the paralysis is limited to a limb which has recently been the site of an injury, for example, a fracture. The widespread use of prophylactic inoculation in children was followed by the observation that such injections were occasionally followed by localized paralysis of the limb inoculated. This question was investigated statistically in 1949 by Hill and Knowelden (1950). They concluded that the distribution of the bodily sites of paralysis was quite abnormal in children who had been inoculated within the months preceding the onset of their illness, namely the distribution in the recently inoculated was in accordance with the customary inoculation procedure in this country. In the recently inoculated children the limb of injection was a site of paralysis much more frequently than was the case with children not recently inoculated. This effect appeared to be confined to injections given within about a month of the onset of poliomyelitis. After that interval from inoculation has elapsed no risk need be envisaged. In view of the suggestion that the recent injection of an antigen merely localized an already developing paralysis in that particular limb of the child the authors point out that the contrast of the poliomyelitis cases with specially collected and paired control children indicated that there might be present in the poliomyelitis group cases which would not have been clinically diagnosed as poliomyelitis at all if the inoculation had not brought them into the paralytic group. Burnet (1950) also reached the conclusion that there could be no doubt that there was a significant relationship between the injection of a pertussis or combined antigen and the subsequent appearance of moderate to severe paralysis in the limb injected. He drew from his figures the conclusion that there was no more than a strong probability that diphtheria APT injection had a similar less intense effect. He felt that in the present state of our knowledge pertussis immunization should cease for any period in which there was the highest incidence of poliomyelitis in the

community concerned, but that diphtheria immunization was so important to the community that only very clear evidence of the occurrence of harmful sequelæ should be allowed to interfere with the policy of universal immunization.

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THE COXSACKIE VIRUSES

The Coxsackie viruses comprise a group which at present include some fifteen strains and are so called because the first of such viruses to be identified was isolated in 1947 by Dalldorf and Sickles by the inoculation of suckling mice with stool extracts from two children in the village of Coxsackie, N.Y. Since then numerous isolations of Coxsackie virus have been made in various parts of the world. The pathological changes observed in animals, particularly in suckling mice, have shown that strains of Coxsackie virus can be arranged in three groups (1) those which cause chiefly myositis, (2) those which do not involve skeletal muscles but affect the myocardium, liver, fat, and central nervous system and (3) strains producing lesions in skeletal muscle and in viscera. The Coxsackie virus is one of the smallest viruses, the particles probably measuring about 20 μ in diameter.

Symptomatology

The incubation period of Coxsackie infection is between two and ten days, commonly three to five days. Several distinct syndromes have been described, but in many cases there is a combination of various features.

Epidemic Pleurodynia. Epidemic pleurodynia, or Bornholm disease, has been known in European countries for many years. Recently outbreaks of a condition clinically similar have occurred in the United States and evidence of Coxsackie infection has been obtained in several persons. This illness is characterized by fever, headache, cough, vomiting, sore throat and pain in the diaphragmatic region, chest or abdomen. Some of the patients have had a pleural rub. A febrile illness characterized by abdominal pain and muscular rigidity may lead to the erroneous diagnosis of an acute abdomen.

Influenza-like Symptoms. In some case the virus has been shown to be responsible for an acute illness of short duration characterized by fever, pain in the muscles and sore throat, sometimes accompanied by headache.

Herpangina. This clinical picture, also attributable to the Coxsackie virus, is characterized by sudden onset with fever, sore throat, headache and abdominal pain. On examination small punched-out ulcers can be seen on the anterior pillars of the fauces, the hard and soft palate or the tongue. These ulcers have grey bases and the surrounding tissue is red. Most affected individuals have been young children.

Meningitis. As stated above, the Coxsackie virus may invade the nervous system of animals and there seems little doubt that it can produce in man a clinical picture of "acute aseptic meningitis" (Hummeler, Kirk and Ostapick, 1954). These cases have mostly occurred in summer or autumn at the same time as poliomyelitis is often prevalent. The cerebrospinal fluid contains an excess of cells, usually mainly lymphocytes, with corresponding increase in the protein content.

Prognosis. The prognosis of Coxsackie infections is good. The course of the illness is usually short and recovery is complete. No specific treatment is known.

Diagnostic Tests. The diagnosis can only be established by the isolation of the virus from the nasopharynx or stools, or the demonstration of virus-neutralizing and - complement-fixing anti-bodies in the blood serum.

**The Co-Existence of Poliomyelitis
and Cocksackie Viruses**

From what has been said it will be clear that infection with the Cocksackie virus may simulate either the abortive phase or the non-paralytic phase of poliomyelitis. To add to the difficulties of diagnosis it has been shown that outbreaks of the two infections may occur at the same time in the same locality and a number of workers have isolated both poliomyelitis and Cocksackie viruses from the same specimen of stool. It has also been demonstrated that in such persons a rise in both poliomyelitis and in Cocksackie antibodies may develop. It would seem, therefore, that a true double infection may occur and this co-existence of poliomyelitis and Cocksackie viruses has been demonstrated in carriers, sufferers from abortive type illnesses, cases of aseptic meningitis and, finally, from cases of bulbar and spinal paralysis.

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CHAPTER 8

DEMYELINATING DISORDERS

Acute Disseminated Encephalomyelitis

Pathology. The pathology of acute disseminated encephalomyelitis has been too long well recognized to need description in detail here. Only a brief summary will be given as a basis for the discussion of ætiology which follows. The pathological picture is characterized by perivascular, and especially perivenous, inflammatory infiltration of the brain and spinal cord. Although there is an infiltration of the perivascular spaces with round cells, lymphocytes, plasma cells, etc., this feature is inconspicuous compared with the extensive zones of infiltration around the vessels at a greater distance. In the white matter, the vessels, and especially the veins, are often surrounded by conspicuous zones of demyelination with relatively little cellular infiltration. Although the white matter is thus markedly affected, the grey matter suffers even more, and the whole nervous system shows evidence of inflammation in severe cases from the cerebral cortex to the sacral region of the spinal cord. The pathological changes, however, may be localized, for example, chiefly to the spinal cord.

Experimental Demyelinating Encephalitis

Much work has been done recently in elaboration of the observations first made by Rivers and Schwentker that a demyelinating encephalitis could be produced in monkeys by repeated injections of brain material (Bailey and Gardner, 1940, Kabat *et al.*, 1947, Morgan, 1947, Morison, 1947, Wolf *et al.*, 1947, Lumsden, 1949 a and b). This form of encephalitis can be produced regularly in a high proportion of animals by a single subcutaneous injection, or a short series of injections, of sterile normal brain tissue from either homologous or heterologous species suspended in an oily adjuvant containing the products of killed tubercle bacilli. The disease can also be produced, though with less certainty, by the injection of brain tissue without the adjuvant. The animal's own brain tissue removed by operation and injected subcutaneously will produce the lesion (Kabat *et al.*, 1949). The circumstances of the experiments exclude the possibility that a

transmissible virus is responsible and the effective agent is not a protein. Lumsden (1949b) has shown that it is extractable with the myelin sheath lipoids, sphingomyelin and cerebrosides and not with the axonic lipoids, lecithin and cephalin. Colover (1954) has shown which tubercle bacillus fractions are active in producing demyelinating encephalitis.

The lesion produced in animals so inoculated is remarkably uniform throughout all species. It consists, according to Lumsden, of severe disseminated perivascular—essentially perivenular—partial softenings in the white matter with a sharp microglial reaction and a proliferative response of the adventitial histiocytes in the vessel walls. The perivenular partial softenings appear in myelin preparations as sleeves of demyelination and several lesions may become confluent so that widespread disintegration occurs within the centrum ovale. Though the central veins and venules may be much engorged there is no thrombosis. Lumsden states that when opportunity is given to examine the late results of the lesion these are seen to be glial and mesodermal scars and there is no evidence of production of any spreading demyelination at all comparable to multiple sclerosis. While, then, this experimental disease does not reproduce multiple sclerosis it has at least a remarkable similarity to acute disseminated encephalomyelitis of the post-exanthematous type in man.

Lumsden (1949a) discussing the close parallelism between experimental encephalitis and human post-exanthematous encephalitis, says "it is an attractive hypothesis that this latter lesion is due not to the virus of the original disease but to some chemical derivative of the skin rash (whether or not sensitization is involved) a chemical substance closely allied to, if not identical with, the chemical derivative of brain and nerve tissue which is responsible for the experimental lesion."

Hurst (1941a) put forward the view that demyelination must be mediated by enzymatic processes and this idea has been further developed by Lumsden (1950). He studied the lesions of the central white matter of the brain produced in rats by chronic KCN poisoning. These symmetrically placed lesions have peculiarities which distinguish them from vascular, asphyxial and other toxic conditions in the rat and from the similar lesions which occur in the human brain. Lumsden points out that in cyanides we are dealing with toxins which have a special affinity for the central white matter of the brain and which are potent enzyme poisons. The striking feature, however, is that the cerebral lesions produced

by experimental cyanide intoxication develop suddenly and are irreversible, progressing uniformly to death. This suggests the possibility that demyelination is a secondary phenomenon and that the toxic, or lytic agent, which ultimately does the damage to the white substance, is not the cyanide itself but one derived and spreading from a central focus in the white matter.

Ætiology of Spontaneous Disseminated Encephalomyelitis. When acute disseminated encephalomyelitis was first recognized stress was naturally laid upon the acute exanthemata with which it appeared usually to be associated and it was consequently spoken of as post-vaccinal encephalitis, smallpox encephalitis, measles encephalitis and so on. It soon became recognized, however, that no pathological differences existed either between the encephalitides following the various exanthems or between them and acute disseminated encephalomyelitis following a banal infection, such as influenza, or even occurring spontaneously without any evident precipitating cause. It is now generally accepted that acute disseminated encephalomyelitis when it follows an exanthem is not directly due to the causative virus of the exanthem, nor is there believed to be some other virus common to all forms of acute disseminated encephalomyelitis whatever their precipitating cause may be. The common disorder of function which is to be held responsible for the common pathological picture must therefore presumably be some disturbance which intervenes between the initial infection, vaccination, smallpox, measles, etc., and the changes in the nervous system. This view receives support from the experimental production of acute disseminated encephalomyelitis by the methods described above.

Miller and Evans (1953) state that there is "growing evidence that acute disseminated encephalomyelitis represents a non-specific allergic reaction of the nervous system to varying antigens, chiefly of bacterial or virus origin, though possibly of other kinds as well." In support of this view they point out that acute encephalomyelitic syndromes, in every way similar to those occurring spontaneously, are occasionally encountered in serum sickness, following a variety of prophylactic inoculations and, in rare instances, in association with angioneurotic oedema, urticaria, purpuric eruptions and acute glomerulonephritis. While the recurrence of acute disseminated encephalomyelitis is almost unknown in those cases in which the initial illness follows one of the specific fevers, recurrence is most likely to occur when the

nervous disorder follows a non-specific minor infection, usually of the upper respiratory tract, in which, as Miller and Evans point out, the development of lasting immunity is known to be exceptional and in which repeated antigenic insults furnish a possible pathogenetic mechanism.

Symptomatology. There is no clinical feature which distinguishes acute disseminated encephalomyelitis following vaccination or one of the specific fevers from the spontaneously occurring variety. The following account of the symptoms of spontaneous acute disseminated encephalomyelitis given by McAlpine (1931) is true of both. McAlpine reviews the clinical picture and draws attention to the abrupt onset, frequently associated with fever, and the not uncommon occurrence in children of headache and meningeal signs. He regards as highly characteristic the way in which fresh neurological symptoms appear, usually within the first three weeks, but in rare instances up to some few months from the onset, and the rapid recovery which takes place, even when there has been evidence of severe involvement of the central nervous system. This recovery is usually complete, though in some instances sequelæ remain. The mortality rate is low. McAlpine distinguishes a cerebral type, characterized not uncommonly by meningeal symptoms and convulsions, with focal signs such as hemiplegia, hemianopia or aphasia, and a spinal type in which pain is an early and striking feature, and paræsthesiæ not uncommon. Motor weakness in the lower limbs, which may progress to complete paraplegia, is usually noticed within a day or two of the onset, but may not appear until the end of two or three weeks. The deep reflexes may be exaggerated or abolished, and the plantar reflexes are usually extensor. Disturbances of sensibility occur in about half the cases. There may be a diminution of all forms below a certain level, or a dissociated sensory loss, in which case appreciation of pain, heat and cold is most frequently impaired. Sphincter disturbance is common. The spinal cord picture may be complicated by the presence of nystagmus and ataxia. The upper cranial nerves commonly escape, though optic neuritis may occur, and is then not uncommonly bilateral. The association of bilateral retrobulbar or optic neuritis with myelitis, occurring after vaccination or measles, is of interest when considering the relationship between acute disseminated encephalomyelitis and neuromyelitis optica (Devic's disease). It is probable that some cases at least of spontaneously occurring acute bilateral optic or retrobulbar neuritis, without any other signs in

the nervous system, are examples of acute disseminated encephalomyelitis. Changes in the cerebrospinal fluid are inconstant; a moderate increase of lymphocytes may be found.

Relationship to Disseminated Sclerosis. The relationship between acute disseminated encephalomyelitis and disseminated sclerosis has been much discussed, and the subject has been reviewed by Spiller (1929), Brain (1930), Grinker and Bassoe (1931), Ferraro (1937) and Hassin (1938). Many writers believe that acute and rapidly fatal forms of disseminated sclerosis occur with histological features identical with those of recent patches of the chronic form. Turnbull (1928) has stated: "I find it impossible to consider acute and chronic disseminated sclerosis to be other than varieties of one condition: transitions between the two and mixtures of the two have been the rule rather than the exception in my experience". Since all graduations of clinical acuteness occur in disseminated sclerosis, there are both clinical and pathological grounds for accepting the existence of an acute form of this disease. On the other hand, the pathological picture of acute perivascular myelinolysis, when occurring as a sequel of the exanthemata and vaccination, is histologically distinguishable from the acute forms of disseminated sclerosis and is associated with clinical points of difference.

Since acute disseminated encephalomyelitis following the specific fevers is normally a self-limited disease, there are clinical as well as pathological grounds for distinguishing it from disseminated sclerosis, and if spontaneous acute disseminated encephalomyelitis is the same disorder it, also, is nosologically distinct from the progressive disease. And this remains true even though spontaneous acute disseminated encephalomyelitis may occasionally follow for a time a relapsing course, as pointed out by McAlpine and more recently by Miller and Evans.

If this is so it makes it all the more important to endeavour to distinguish acute disseminated encephalomyelitis from the acute stage of disseminated sclerosis. McAlpine draws attention to the following points as being of diagnostic value:—

(1) A temperature of over 100°F. is in favour of acute disseminated encephalomyelitis.

(2) Severe shooting pains rarely occur in acute disseminated sclerosis, but are common in acute disseminated encephalomyelitis.

(3) Diplopia, common in disseminated sclerosis, is rare in acute disseminated encephalomyelitis; in the latter condition nystagmus,

when present, is finer and more rapid than that seen in disseminated sclerosis. Retrobulbar neuritis may occur in both conditions, but is more frequent in disseminated sclerosis, when it is usually unilateral; in acute disseminated encephalomyelitis both eyes are generally affected.

(4) Euphoria, which is common in early disseminated sclerosis, is rarely, if ever, met with in disseminated encephalomyelitis.

(5) Sensory loss in disseminated sclerosis, when present, commonly involves postural and vibration sense; in acute disseminated encephalomyelitis thermal and, to a lesser extent, pain sensibility may be affected.

(6) Loss of the deep reflexes in the lower limbs is not uncommon in acute disseminated encephalomyelitis, but it is of rare occurrence in disseminated sclerosis.

After the acute stage has subsided, if the patient is found to have residual physical signs, the diagnosis from disseminated sclerosis may be extremely difficult. It must be based upon the history of the onset and development of symptoms in the acute stage and the absence of any extension of the physical signs after the first few weeks of the illness.

Acute Hæmorrhagic Leuco-Encephalitis

Hurst (1941b) described as acute hæmorrhagic leuco-encephalitis a pathological picture not previously reported and gave an account of two cases. Single cases have since been reported Henson and Russell (1942) and Greenfield (1950). The parts of the nervous system chiefly affected are the central areas of the centrum semiovale. Macroscopically there are œdema and small hæmorrhages. Microscopically the characteristic features are polymorphonuclear exudation around the vessels, perivascular zones of partial or more complete necrosis and fibrinous exudate into and through the vessel walls. Hurst suggested that the hæmorrhagic lesions and the non-hæmorrhagic areas of necrosis or demyelination represent different degrees of injury by a single noxious agent, and that acute hæmorrhagic leuco-encephalitis may form a link between the demyelinating diseases and some forms of so-called hæmorrhagic encephalitis. Greenfield (1950) believes that acute hæmorrhagic leuco-encephalitis is nosologically identical with acute disseminated encephalomyelitis, the two representing different grades of intensity of reaction to a similar pathological process. Somewhat similar pathological changes

were reported in the cases of acute meningo-encephalomyelitis of childhood described by Brain and Hunter (1929).

Patients with acute hæmorrhagic leuco-encephalitis develop a febrile illness, characterized either at once or after a brief remission, by headache, vomiting, and deepening stupor with or without hemiparesis. The blood shows a polymorphonuclear leucocytosis and the cerebrospinal fluid is characterized by a high cell count with many polymorphonuclear cells.

At present the diagnosis of acute hæmorrhagic leuco-encephalitis can only be made with certainty upon autopsy material. It must not, therefore, be concluded that the disorder is invariably fatal. Probably it is not, and patients may survive the attack with varying degrees of disability.

Treatment

No specific treatment for either acute hæmorrhagic leuco-encephalitis or acute disseminated encephalomyelitis is known. When the latter disease follows an exanthem, convalescent serum, if obtainable, can be given, but its value is doubtful, and today it may not be free from the risk of conveying homologous serum jaundice. Gamma globulin may be of value. Miller (1953) has used ACTH for the treatment of acute disseminated encephalomyelitis and this substance, and cortisone, may be of value in combatting the local effects of the inflammation, though Miller stresses the importance of a correct diagnosis before using drugs which in other disorders are potentially harmful.

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Neuromyelitis Optica

Neuromyelitis optica, a demyelinating disease characterized by the association of bilateral acute optic or retrobulbar neuritis and myelitis, continues to give rise to discussion. Debate centres upon the question of its relationship to disseminated sclerosis on the one hand and acute disseminated encephalomyelitis on the other. Though this may seem an academic question, an answer to it could not fail to throw light upon the nature of the demyelinating diseases in general. But it is by no means an academic question in the individual case in relation to prognosis.

McAlpine (1938) reviews the pathological diagnosis of neuromyelitis optica, adding ten further pathological reports from the literature, together with the two of his own, to the twenty-five collected by Beck (1927). The characteristic lesion is a diffuse demyelination going on to necrosis and sometimes accompanied by cavitation. In some cases, however, instead of a diffuse pathological process there are disseminated foci. In the most affected areas, destruction of axis-cylinders is the rule. Usually there is a relative absence of gliosis. A true inflammatory reaction usually occurs in the acute phases of the disease, but is slight or absent in the more chronic cases. In his own cases the pathological process was limited to the spinal cord, optic chiasma, optic tracts and optic nerves. In No. 1 there was marked demyelination of the optic nerves, and in No. 2 there was a diffuse demyelination of the optic nerves, optic chiasma and the initial portion of one optic tract. In both there was a diffuse myelitis extending from the cervical region to approximately two-thirds of the dorsal cord. Macroscopically, in both there were several segments of the mid-dorsal region of the cord in which the cut surface appeared a dark brown in colour; the substance of the cord was soft and diffuent, and there was no distinction between the white and grey matter. The demyelinating process had thus advanced to necrosis. In

No. 2 the glia was little affected and gliosis was absent or slight. In No. 1 the macroglial response was more definite; in both cases there was a brisk microglial response. Perivascular and meningeal infiltration with lymphocytes was evident at both cervical and mid-dorsal levels of the cord in No. 2, but was absent in No. 1.

The clinical features are discussed by McAlpine and have more recently been reviewed by Stansbury (1949), who collected over 200 cases from the literature, and Scott (1952). Scott reports ten new cases which came under his own observation. He points out that in a large proportion of cases the onset of visual loss or of myelitis is preceded by either a sore throat, a "cold in the nose", a febrile disturbance or headache with or without a general feeling of malaise. In his experience optic neuritis is much commoner than myelitis as the first major incident, but in a certain proportion of such cases an accurate history may reveal the occurrence in the past of symptoms of transient involvement of the cord. A study of 50 cases which he made showed optic neuritis as the first major event in 30 cases and myelitis as the first in 20. He gives his impression that in cases in which optic neuritis is the first major symptom, without preceding or very early signs of involvement of the cord, the prognosis is rather better than in those in which myelitis is the first major symptom. He found no relationship between the severity of the optic neuritis and that of the myelitis.

He believes that, in the past, excessive concentration upon fatal cases in which pathological material has been available has led to an unbalanced clinical picture and he lays stress upon the importance of including abortive cases. In addition to the classical picture of the disease he mentions a second, and, in his opinion, larger group of patients, in whom there is bilateral optic neuritis, but in whom signs of myelitis, although quite definite, are much less obvious with little affection of the motor pathways. He would also include cases mentioned by Walsh (1925) in which the ocular manifestations occur alone.

Changes in the cerebrospinal fluid are of some diagnostic importance. McAlpine states that, in over 50 per cent of cases and in a higher percentage of the rapidly progressive type, there is increase in cells, mainly polymorphonuclear, a point also stressed by Balser (1936). The protein is moderately raised. The Lange and benzoin curves are almost constantly negative in all stages of the disease, a point of distinction from disseminated sclerosis.

Both McAlpine and Scott make a similar division of cases in respect of the course of the disease into three groups, namely,

(1) those cases in which the patient dies in from a few days to several weeks after the onset. (2) Those cases in which one or more remissions occur, but the patient finally dies from some months to two or three years after the onset and (3) finally, those patients who recover completely or partially.

Whether neuromyelitis optica is a nosological entity, and what is its relationship to disseminated sclerosis and acute disseminated encephalomyelitis, must at present be decided, if it can be decided at all, upon clinico-pathological grounds, since we do not know the aetiology of any of the three. Hassin (1937) considers that neuromyelitis optica is a definite morbid entity, different from both disseminated sclerosis and disseminated encephalomyelitis. McAlpine shares this view, but Ferraro (1937) thinks that neither on clinical nor on pathological grounds can neuromyelitis optica be distinguished from acute disseminated sclerosis and acute disseminated encephalomyelitis. Scott believes that neuromyelitis optica is on clinical grounds distinguishable from disseminated sclerosis, but more difficult, especially in its atypical forms, to differentiate from acute disseminated encephalomyelitis. Miller and Evans (1953) on both clinical and pathological grounds adopt a similar view.

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Disseminated Sclerosis

It cannot be said that the experimental work on demyelinating disorders has thrown any new light upon the age-long problem of the aetiology of disseminated sclerosis. Nevertheless, the patient accumulation of facts and statistics has continued, and, it is to be hoped, will in time contribute to that end and meanwhile makes valuable information available to the clinician. McAlpine and Compston (1952) have published a study of the natural history of the disease. They first consider the incidence of disseminated

sclerosis in the United Kingdom. Using figures for the mortality rate and the average duration of life they reach the conclusion that there is a prevalence rate in England and Wales of approximately 1 in 2,400 of the population and in Scotland of 1 in 1,570. Their figures support the generally accepted view that there is in the United Kingdom a slight excess of females over male patients.

Familial Incidence. Pratt, Compston and McAlpine (1951) have studied the familial incidence of disseminated sclerosis. In a total of 310 cases this was 6·5 per cent. The incidence of disseminated sclerosis in the sibs of 168 cases and in the parents of 310 cases was significantly higher than that expected on the basis of a random distribution of the disease. Striking examples of familial incidence were the occurrence of the disease in a mother and four of her daughters and an example of the disease occurring by direct transmission in three generations. The authors conclude that their studies support the view that a genetic factor is present in disseminated sclerosis, and that there is evidence pointing to both a dominant and a recessive mode of inheritance.

Course and Prognosis. McAlpine and Compston have studied the course of the disease in 475 of their patients. Of these 21 suffered only a single progressive episode and a further 22 had a progressive symptom from the onset, but other symptoms remitted: 393 patients at some time or other had episodic features in their course, although in many it sooner or later became chronically progressive. The material was analysed to show the average yearly attack rate which was approximately 0·40 attacks per year for patients of either sex. The average attack rate showed a slight fall after the first ten years.

The authors found that approximately 35 per cent of patients having a second attack did so within one year, 54·5 per cent within two years and 75 per cent within five years of the onset of their disease. The first remission may last fifteen years or more (19 patients, 5·3 per cent). The longest remission in their series was thirty-seven years. Of the 19 patients whose remission lasted fifteen years or more, 13 (68·4 per cent) had commenced their disease with retrobulbar neuritis, whereas only 31·9 per cent of all patients analysed did so.

Investigation of the chronic progressive stage showed that of 146 patients running a chronic progressive course, 43 did so from the onset and 103 after a preliminary relapsing course. A course progressive from the onset might occur at any age from the twentieth year onwards. The prognosis as to life has been studied

by Allison (1950) who found that the average duration of the disease was approximately twenty years in the case of those patients who had died. Inclusion of survivors suggested that the average for the whole series would be somewhat greater than twenty-two years. McAlpine and Compston agree that it seems probable that the average duration of life is at least twenty years. Both Allison and McAlpine and Compston mention the occurrence of a terminal status epilepticus.

Factors Affecting the Onset and Course. McAlpine and Compston have investigated a consecutive series of 250 cases with the object of ascertaining whether they could discover any factors which might influence the onset and course of the disease. They obtained a history of trauma during the three months preceding the appearance of the first symptoms of the disease in 36 cases (14·4 per cent). In 31 patients out of a total of 146 who suffered injury more than three months before the onset of their disease the site of the initial lesion was related to the site of injury (21·2 per cent). These figures are considered to be significant. A tendency for superficial infection to determine the site of the initial lesion is also noted. Pregnancy did not appear to be of importance in relation to onset or relapse. The incidence of allergic disease was significantly increased in the disseminated sclerosis group (27 per cent) compared with the control group (16·8 per cent).

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CHAPTER 9

THE INTERVERTEBRAL DISC AND SPONDYLOSIS

THE importance of the intervertebral disc in neurology is a recent discovery. Shortly before the war the observation was made that a protruded lumbar intervertebral disc was the commonest cause of sciatica; more recently attention has been drawn to the importance of disease of the cervical intervertebral discs as a cause of brachial neuralgia and of a myelopathy which may simulate a large number of chronic disorders of the spinal cord. Though the intervertebral discs may be involved in a number of pathological states of the spine, including infections and neoplasms, this chapter will be concerned only with acute and chronic protrusions of intervertebral discs and the associated changes in adjacent vertebræ. (Brain 1954 a and b. Cave *et al.*, 1955, Clarke 1953, *Lancet* leader, 1955).

THE CERVICAL INTERVERTEBRAL DISC

Anatomy

Certain points in the anatomy of the cervical spine are of importance for the explanation of the pathology and symptomatology of lesions of the cervical intervertebral discs. The atlas and the axis differ from the other cervical vertebræ in that the spinal nerves emerge posteriorly to the occipito-atlantal joint and the corresponding joint between the atlas and the axis. There is no intervertebral disc between the atlas and the base of the skull nor between the atlas and the axis. Intervertebral discs are placed between the remaining cervical vertebræ and are identical in structure with those in the dorsal and the lumbar regions of the spine. The intervertebral foramina through which the spinal nerves emerge between the 2nd and 3rd, 3rd and 4th, 4th and 5th, 5th and 6th and 6th and 7th cervical vertebræ are bounded above and below by the pedicles of the two adjacent vertebræ. The radicular nerves are situated in the foramina, and the dorsal root ganglia lie just outside in the gutter of the transverse process. The

posterior wall of the foramen is formed by the superior articular process of the vertebra below, which, in turn, is covered posteriorly by the inferior articular process of the vertebra above. The ventral delimitation of the foramen is effected partly by the two adjacent vertebral bodies and partly by the dorso-lateral rim of the intervertebral disc. This is termed the uncinat process, and there has been some discussion as to whether between the uncinat process of the lower vertebra and the corresponding facet of the vertebra above there is a true joint, as Luschka supposed. This has been called the uncovertebral joint and the neuro-central joint, but some, including Frykholm (1951b) believe that what has been regarded as a joint cavity is merely part of the annulus of the intervertebral disc.

The rather complicated structure of the investment of the radicular nerves can be best understood by reference to a diagram (Fig. 4). Opposite each foramen the dural sac has a small infundibular extension, the dural root-pouch, or axillary pouch of some authors. By means of the funnel-like shape of the pouches, each nerve-root is conveyed in a smoothly curved course to the point at which it leaves the dural sac. At the bottom of the root-pouches there are two openings, the dural root-ostia, one ventral and one dorsal, which are separated by a small dural septum, the interradicular septum. Each root-ostium leads into an individual root-sleeve, of which there are consequently two, one dorsal and one ventral. The root-sleeves, which are lateral extensions of the dural sacs, are separated by a small cleft known as the interradicular foramen. Consequently, outside the dural sac, the dorsal and ventral roots pass through individual sheaths which are entirely separated. A tubular extension of the arachnoid membrane encloses each root in its proper root-sleeve. Between the dural sac and the dorsal root ganglion the two roots lie close together and form an anatomical entity referred to as the radicular nerve. The radicular nerve normally occupies only one-fifth to one-fourth of the diameter of the foramen, hence, if the nerve lay always in the middle, considerable narrowing of the foramen could occur without producing any effect upon it. Frykholm (1951c), however, points out that the morphology of the lower cervical radicular nerves and their root-pouches is extremely variable. In early childhood the dural sac and the radicular nerves are only loosely attached to the bone. As age advances they gradually become relatively well fixed in their definite positions. In most cases the radicular nerves then take a slightly downward course

and pass through the centre of their respective foramina. Variations in this arrangement may occur in normal individuals, probably as the result of disproportionate growth of the dural sac and the cord relative to the vertebral column.

Pathology and Ætiology of the Bony Changes

Brain (1948) distinguished two types of disc protrusion and this has been confirmed by Frykholm (1951a) in his comprehensive monograph on intervertebral disc degeneration. These are (1) the nuclear herniation and (2) the annular protrusion. The first type, which forms a well-localized mass, is due to the extrusion of nuclear material through a tear in the annulus fibrosus. The second type, which may be either localized or diffuse, is due to the bulging of the annulus. A nuclear herniation is originally soft, but may be transformed into a fibrous or cartilaginous mass in which calcification may occur. An annular protrusion is originally fibrocartilaginous, but may gradually become similarly calcified. The causes of these two types of protrusion are different. A *nuclear herniation* is the result of a weakness of the annulus fibrosus relative to the strain put upon it by a movement of the neck. When the movement is itself not abnormal in range or violence it is probable that there is a pre-existing weakness of the annulus fibrosus. In such cases the herniation may be described as spontaneous. When, however, the neck movement is itself violent, a nuclear protrusion may occur through rupture of a normal annulus fibrosus and such cases are classified as traumatic.

The production of an *annular protrusion* is different. Owing to various factors, of which age is probably the most important, the intervertebral disc becomes dehydrated and loses its elasticity. As a result it collapses and the annulus bulges in all directions. Local bulgings may also occur at some point if the fibres of the annulus are less resistant. The protruded material becomes vascularized and its fibrous elements are increased in the same manner as in the nuclear herniation. Similarly the added tissue increases the size of the original protrusion, and again calcification or ossification may occur. (Figs. 5 and 6).

So far we have been describing the alterations which occur in the intervertebral discs themselves, but the impairment of their normal functions leads to reactive changes in the bodies of the adjacent vertebræ. These are stimulated to new bone formation, i.e. the production of the osteophytes which tend to fuse with the disc protrusions. Frykholm distinguishes two types of osteophytes:

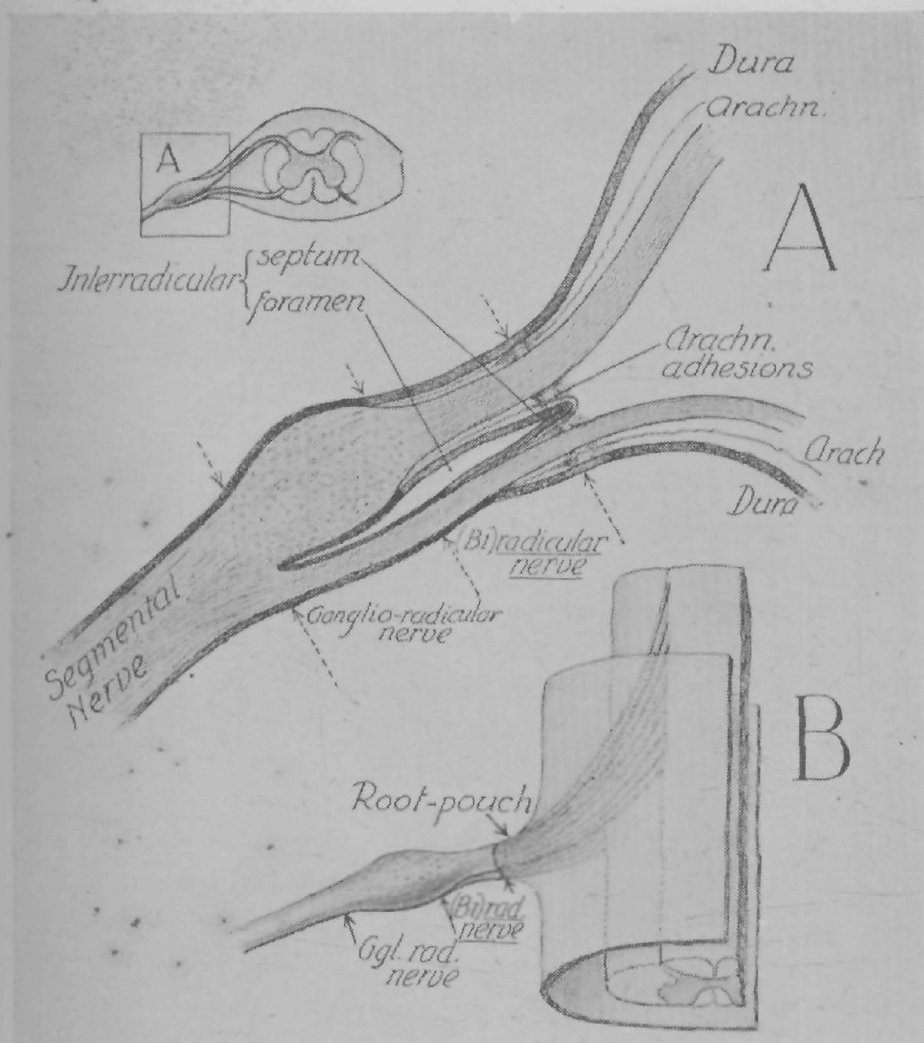


FIG. 4. Drawing showing principal features of the anatomy of cervical nerve-roots and their dural and arachnoidal investments (Frykholm, 1951c). For details see text. (*The Lancet*.)

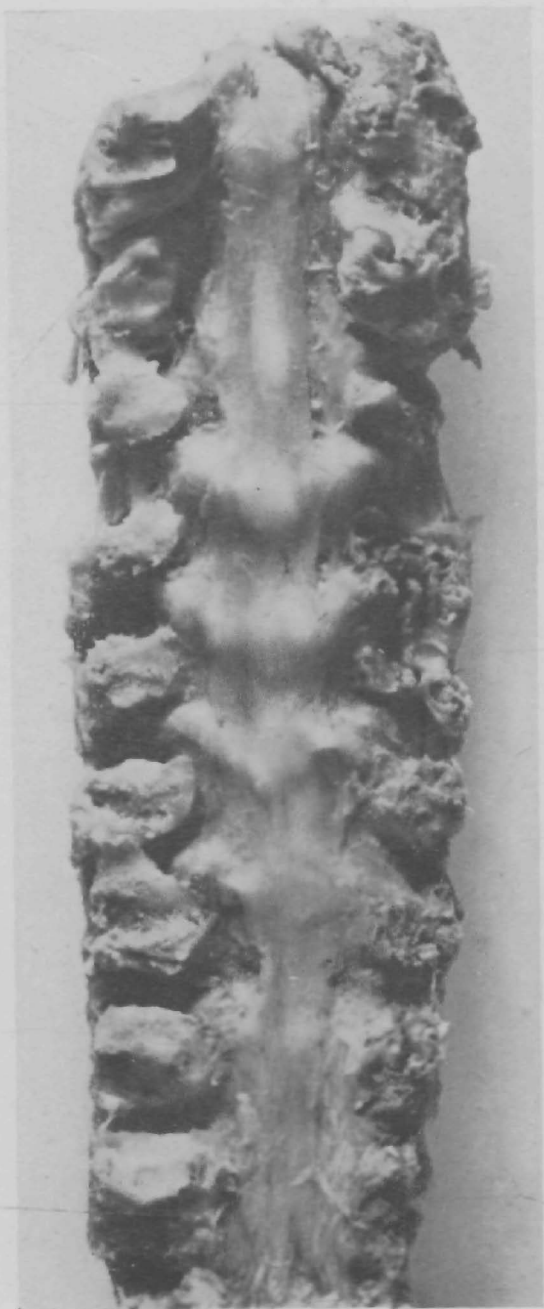


FIG. 5. Posterior aspect of cervical spine showing disc protrusions. (*Annals of the Rheumatic Diseases.*)



FIG. 6. Cervical spine divided sagittally to show disc degeneration and annular protrusions. (*Annals of the Rheumatic Diseases.*)

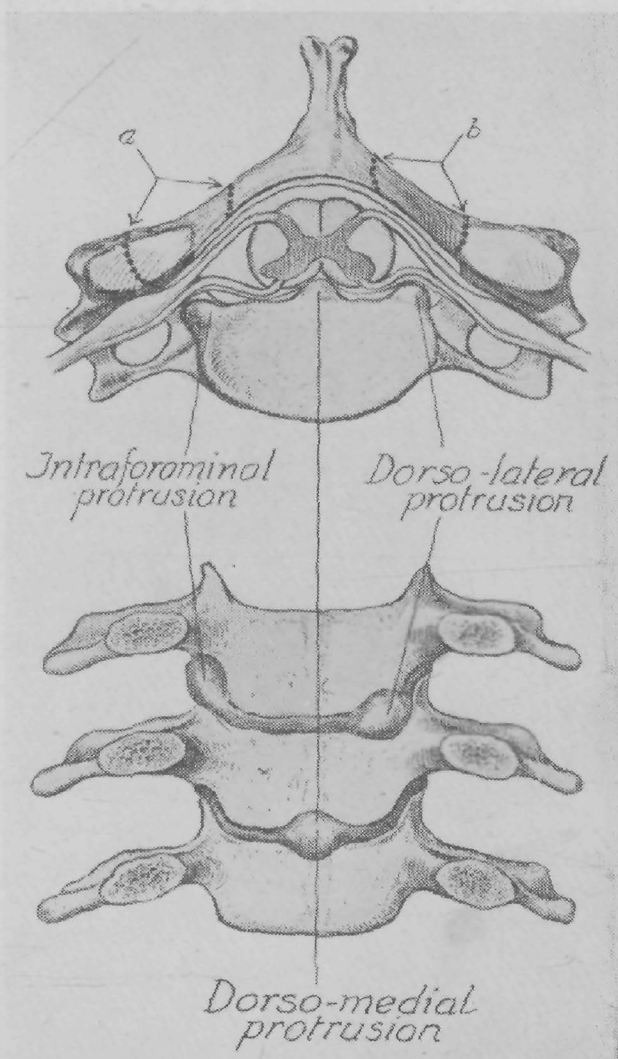


FIG. 7. Drawing (Frykholm, 1951b) showing principal types of disc protrusion: (i) dorsomedial; (ii) dorsolateral; and (iii) intraforaminal. (*The Lancet.*)

the one which is produced in the manner just described he calls marginal lipping, which may either be localized or affect the entire circumference of the vertebral margins. Ventral spurs, on the other hand, are anatomically related to the anterior longitudinal ligament and, according to Schmorl (1929), they are the result of increased strain on this ligament, the fibres of which are firmly attached to the vertebral margins. Furthermore, the collapse of a disc also results in subluxation of the corresponding intervertebral joints with secondary osteophyte formation on the articular processes, which leads to further narrowing of the intervertebral foramina.

The pathological changes of cervical spondylosis may involve one pair of intervertebral joints or more than one. When the joint lesions are multiple the joints affected may be adjacent to one another, or they may not. The spondylosis may affect the cervical spine alone, or may be part of a generalized process involving to a greater or lesser extent the whole spine. A combination of cervical and lumbar spondylosis is not rare, so that patients are encountered who suffer successively, or even simultaneously, from sciatica and the symptoms of cervical spondylosis.

Since age is the chief factor in causing the degeneration of the intervertebral discs, most patients are middle-aged or older. The average age of onset of symptoms in the series reported by Brain, Northfield and Wilkinson (1952) was 49, three-fifths of their patients being between 40 and 59 when symptoms began. Males were affected more than twice as frequently as females. Only 20 to 30 per cent of patients give a history of trauma which might have contributed to the disc degeneration. Congenital abnormalities of the cervical spine, particularly congenital fusion of vertebræ, occur more frequently in patients suffering from cervical spondylosis than in a control group and therefore may be considered as contributory factors.

This degeneration occurs with approximately equal frequency at all levels between the 2nd and 7th cervical vertebræ. It is not, therefore, more common in the lower part of the cervical spine. A protrusion of the disc between the 7th cervical and 1st dorsal vertebræ is rare. One disc is affected alone in one-third of all cases.

Pathology of Nerve-Roots and Spinal Cord

Disc protrusions have been variously classified according to their position in the circumference of the disc, but one or more of these different types of protrusion may be encountered in the

same disc, and they often merge into one another. From the point of view of the radicular nerves and nerve-roots, however, the only two with which we need concern ourselves are the dorsolateral protrusion, which does not invade the intervertebral foramen, but may compress the intrameningeal nerve roots against the vertebral laminae, and the intraforaminal protrusion, which emerges from the uncinat part of the disc and compresses the radicular nerve against the articular processes (Fig. 7). The mechanism of root compression, however, depends not only upon the size and location of the protrusion, but also upon the angulation of the radicular nerve and its situation in the foramen. Thus, for example, a protrusion restricted to the lower part of the foramen may leave the roots quite intact if the radicular nerve is downwardly directed and situated cranially in the foramen, whereas if the nerve is caudally situated and outwardly or upwardly directed there is a much greater chance that it will be implicated. Furthermore, a protrusion which is strictly localized to the lower half of the foramen may produce a selective compression of the ventral root and leave the dorsal root intact, because the ventral root often runs along the caudal border of the dorsal root. Finally, cervical disc degeneration without protrusion may lead to marginal lipping as a result of the increased stress which falls directly upon the vertebræ when the disc loses its shock-absorbing properties. This may cause some osteophyte formation in the anteromedial part of the intervertebral foramen. At the same time narrowing of the disc throws an additional strain upon the corresponding intervertebral joints and that leads to secondary osteophyte formation on the articular processes, thus narrowing the foramen posterolaterally.

The pathological effects of these bony changes in the neighbourhood of the intervertebral foramen have been studied by Frykholm (1951a). In their fully developed form they consist of what he calls "root-sleeve fibrosis". This is characterized by (1) thickening and opacity of the dural root-sleeve and adjacent parts of the dural sac (i.e. the root pouch); (2) narrowing, or complete abolition, of the dural funnel which forms the root pouch; (3) sharpening of the upper and lower duroradicular junction, which sometimes causes a distinct constriction or notching of the radicular nerve; (4) thickening of the dura at the rootostia and occasionally, also, thickening of the intraradicular septum resulting in a constricting ring of fibrous tissue around each nerve-root; (5) thickening and fibrosis of the arachnoid membrane in the neighbourhood of the root ostia, and (6) disintegration and hyalinization of the

dural tissue involved. This chronic constriction of the nerve-roots and radicular nerve, and associated ischæmia, lead in time to the degeneration of the nerve fibres. Frykholm points out that in many cases root-sleeve fibrosis is observed in the absence of any constriction of the corresponding foramen, though in such cases there is usually X-ray evidence of disc degeneration either at the same segmental level or at one or two levels above that of the radicular lesion. Occasionally also root-sleeve fibrosis may be present in spite of the fact that the cervical spine shows no X-ray abnormality.

Thus, cervical intervertebral disc degeneration initiates a complex and variable series of changes which may affect the nerve-roots and radicular nerve in a number of different ways which need to be assessed individually in each case. These changes may be summarized as follows: (1) Disc degeneration affects the mobility of the cervical spine. The simplest example of this is the effect of degeneration of a single disc. Usually this greatly limits flexion and extension at the intervertebral joints between the two vertebræ separated by the affected disc, since the main movement must now occur above and below, and the abnormal stresses may fall not only upon adjacent intervertebral joints but also upon adjacent radicular nerves. Exceptionally, disc degeneration leads to abnormal mobility, in which case, as a rule, the body of the upper vertebra slips forward upon that of the lower on flexion and slips back again on extension, a movement which must obviously tend to produce damage to the radicular nerves in the corresponding foramina. (2) Narrowing of intervertebral discs shortens the cervical spine and disturbs the relationship between the radicular nerves and their corresponding foramina, the lower ones, particularly, tending to rest upon the lower margins of the foramina and to be kinked over them. (3) Disc degeneration by itself can produce lipping of the adjacent vertebral bodies and so narrow the inner margins of the intervertebral foramina, whilst increased strain upon the intervertebral articulations produces osteophytic narrowing posteriorly. (4) All this may occur without intervertebral disc protrusion. In addition, however, a dorsolateral protrusion may compress the nerve roots within the spinal canal, while an intra-foraminal protrusion may compress them or the radicular nerve within the foramen. (5) All the above-mentioned processes tend to lead to root-sleeve fibrosis, the characteristic reaction of the investment of the nerve roots and radicular nerve to chronic irritation and compression. These pathological changes, therefore,

though most likely to occur in the nerve roots which pass through the intervertebral foramina at the level of the degenerated disc, may be present also at other levels at which there is no evidence of disc degeneration. (6) Finally, the affected nerve-roots and radicular nerves, tethered to the foramina by root-sleeve fibrosis, and lacking their normal mobility, are far more susceptible to trauma than normal nervous tissues. Consequently not only may severe and lasting radicular symptoms be set up by head injury in such cases, but it is probable that comparatively slight trauma may be responsible for the acute onset of symptoms in patients with cervical spondylosis and of symptoms which may be multiradicular in distribution although the bony pathological changes may be limited to one intervertebral disc and its adjacent vertebræ.

Cervical spondylosis damages the spinal cord less often than the nerve roots, but sufficiently often to make spondylotic myelopathy one of the commonest, if not the commonest, disease of the spinal cord during and after middle life. This is illustrated by the fact that 41 patients with cervical spondylosis have been admitted as in-patients to the neurological department of the London Hospital during the last two years, mostly on account of myelopathy. The pathogenesis of the myelopathy, like that of the root-sleeve fibrosis, is complex, and certainly a number of factors are concerned. The most obvious is direct compression of the cord by one or more protruding intervertebral discs (Fig. 8). When the disc protrusion is large the cord may be compressed between it and the laminae posteriorly, the pressure being sufficient even to cause thinning of laminae. Greenfield (1953), however, believes that in the majority of cases the areas of demyelination are too limited to be explained as the result of simple compression. He thinks that compression may operate indirectly by interfering with the blood flow through the anterior spinal artery. The blood supply to the spinal cord may be further impaired by narrowing of the intervertebral foramina through which the radicular arteries penetrate. Compression of the anterior spinal veins has also been regarded as a contributory factor. Stretching of the ligamenta denticulata also, in Greenfield's opinion, plays an important part, since by anchoring the spinal cord these ligaments tend to increase the effects of compression on the anterior spinal vessels. Moreover they exert tension on the lateral aspects of the spinal cord. The neck, however, is not static, but in constant movement throughout waking life, and a considerable amount of movement still occurs in

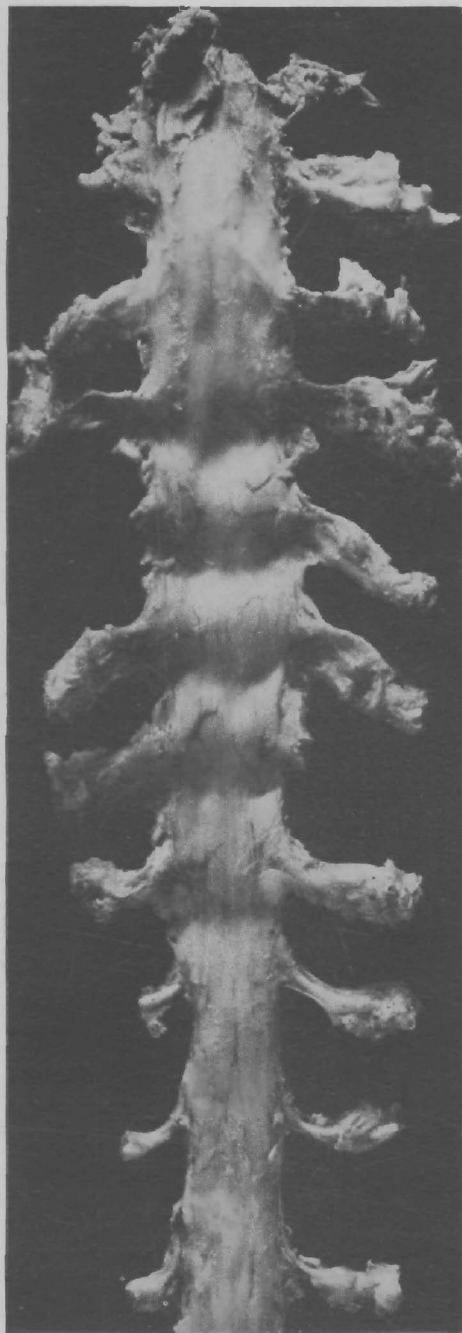


FIG. 8. Anterior aspect of cervical spinal cord showing indentations produced by disc protrusions. (*Annals of the Rheumatic Diseases.*)

a spine which is the site of severe spondylosis. As already mentioned, movement may be pathological when one body slips forward upon the one immediately below it on flexion of the neck. Root-sleeve fibrosis which is invariably present to a greater or less extent in these cases, tends to anchor the roots in the foramina and by thus limiting the mobility of the cervical cord must add to the traumatic effect of repeated movement of the neck when the cord is already compressed by a disc protrusion. All these factors combine to produce a condition which is best described as cervical myelopathy. Moreover, in the presence of cervical spondylosis, even though the spinal cord has so far apparently escaped injury, severe damage may be produced by forcible extension of the neck as the result of a blow upon the front part of the head or even, as Symonds (1953) has recently shown, in the course of the administration of an anæsthetic or an operation upon the tonsils.

Acute Protrusion of the Cervical Intervertebral Discs

Acute protrusion of the cervical intervertebral discs, i.e., herniation of the nucleus pulposus, may occur either (1) spontaneously or (2) as the result of trauma. The traumatic lesion will be considered later.

Spontaneous protrusions usually occur at a younger age than that at which the symptoms of cervical spondylosis manifest themselves, namely, between 40 and 50. The patient usually gives a history of recurrent "cricks" in the neck, attacks of neck pain which have often been diagnosed as "fibrositis". Suddenly, a pain more severe and lasting than the previous ones occurs. The neck may feel as though it is fixed, and both active and passive movement cause an intensification of the pain. The pain is also referred within the distribution of the spinal nerve which is compressed by the invasion of the intervertebral foramen by a laterally placed disc protrusion. Such referred pain extends not only to the cutaneous area of the supply of the spinal nerve, but also to the muscles, bones and joints which the nerve innervates. This area is often much more extensive than the dermatome, for example, an irritative lesion of either the 6th or of the 7th cervical spinal nerve may cause pain to be felt in the pectoralis and latissimus dorsi and serratus magnus muscles on the same side.

On examination of the patient the neck is usually held rigidly and sometimes slightly flexed towards the side of the lesion,

and both active and passive movements cause intensification of the pain. The muscles innervated by the spinal nerve compressed are usually somewhat wasted and hypotonic, but the muscular weakness is usually not severe. The tendon reflexes which they mediate are diminished or sometimes lost. In the acute stage it may be possible to demonstrate some hyperalgesia and hyperæsthesia within the corresponding dermatome or some diminution of cutaneous sensibility. Postural sense is not usually impaired by a lesion of a single spinal nerve. Plain X-rays usually show little abnormal, though there may be slight narrowing of the affected intervertebral disc. Myelography usually shows a filling defect in the column of myodil which is laterally placed in the antero-posterior view and may obliterate the normally filled nerve root-sleeve.

The treatment of spontaneous and acute protrusion of an intervertebral disc involving one spinal nerve is a combination of traction on the head to relieve the pressure upon the protruding disc with immobilization. After the acute phase has passed, immobilization may be continued by means of a plaster collar. If these measures fail, surgical exploration may be required. Spontaneous protrusion of a cervical intervertebral disc must be a very rare cause of compression of the spinal cord. The treatment of such a lesion is that of any other cause of extramedullary compression.

CERVICAL SPONDYLOSIS

Symptomatology

Mode of Onset. The duration of the history of symptoms of cervical spondylosis is extremely variable, ranging from one week to twenty years. In the majority of cases it is less than one year. The general tendency of symptoms of the spinal cord lesion is to develop slowly, but progressively, during the first year or two and then often remain stationary for many years. Indeed, symptoms may even regress if the patient gives up heavy work. Only symptoms due to the radicular lesion are likely to develop acutely or subacutely. In considering the symptomatology of cervical spondylosis it is essential to bear in mind that the symptoms may be either those of a lesion of one or more nerve-roots or spinal nerves, or of involvement of the spinal cord, or of both, so that any level or combination of levels of the cervical spine may be attacked.

It is convenient to consider the radicular and the myelopathic symptoms separately, though they cannot always be sharply distinguished.

Radicular Symptoms. Radicular symptoms may be acute, subacute or insidious in their onset. Acute involvement of one spinal nerve leads to symptoms resembling those of a spontaneous acute protrusion of a single intervertebral disc into the intervertebral foramen, as described above. Pain, however, is not always limited to one dermatome, but may extend down the upper limb to involve to a greater or lesser extent all the digits, in which case a clinical picture resembling the classical one of "brachial neuritis" is produced. An insidious onset is characterized by dysæsthesiæ consisting of burning and tingling sensations, sometimes accompanied by pain, radiating down the upper limb into one or more of the digits and tending to be particularly troublesome at night. Motor symptoms are usually slight or absent: only exceptionally is there a complaint of weakness.

On examination of the patient there may be either hyperalgesia and hyperæsthesia, or hypalgesia and hypæsthesia, within the distribution of the dermatome corresponding to the affected spinal nerve. There may also be localized areas of tenderness in the corresponding muscles. Appreciation of posture and passive movement is usually impaired. There is likely to be slight muscular wasting accompanied by hypotonia in the muscles innervated by the affected spinal nerves, but muscular weakness is usually slight. Only exceptionally is a severe degree of paralysis present. The tendon reflexes mediated by the muscles innervated by the affected spinal nerves are likely to be diminished or lost. The following clinical pictures may be specially mentioned.

(1) **Acroparæsthesiæ.** Acroparæsthesiæ may be defined as unpleasant tingling sensations affecting some or all of the digits of one or both upper limbs, developing during the night and usually passing off within an hour or so of awakening and particularly liable to occur in middle-aged women. Thus defined, acroparæsthesiæ are merely a symptom, and it is inherently unlikely that a symptom of irritation of sensory nerve fibres is characteristic of a lesion occurring at only one point in their course. Acroparæsthesiæ may occur as a symptom of either (1) cervical spondylosis, (2) a costoclavicular syndrome involving particularly perhaps vasomotor elements or (3) compression of the median nerve in the carpal tunnel. Acroparæsthesiæ, however, are so common a

symptom of cervical spondylosis that all patients who complain of them should have their necks X-rayed.

(2) **Pain Referred to Myotome and Sclerotome.** A dermatome is the area of skin supplied by a single spinal nerve. The importance of the dermatome in neurological diagnosis has perhaps tended to obscure the fact that a spinal nerve distributes sensory nerve fibres to muscles, bones, joints and ligaments which have an anatomical distribution ranging widely beyond the cutaneous area innervated by the same segment. The muscles supplied by a single radicular nerve have been termed a myotome and the bones and joints similarly supplied, a sclerotome. Pain due to irritation of a spinal posterior root or radicular nerve, therefore, may irradiate widely, and this may sometimes give rise to difficulties in diagnosis. For example, both the 6th and 7th cervical radicular nerves supply sensory fibres to the posterior cervical muscles, pectoralis major, latissimus dorsi and serratus magnus as well as to other muscles of the trunk and upper limbs and the corresponding dermatomes. Irritation of either of these nerves may therefore cause pain referred to the neck and back and front of the chest as well as to the upper limbs, and, it has been pointed out, may suggest pain of cardiac origin.

(3) **Muscular Wasting.** Muscular wasting is not usually severe as a result of the radicular lesions of cervical spondylosis, but it may be a prominent symptom and even occur in the absence of objective sensory abnormalities. It may then lead to an erroneous diagnosis of motor neurone disease. Frykholm points out that such muscular wasting is probably due to a selective damage to the anterior spinal roots by compression arising from the lower part of the foramina. It may affect the muscles supplied from several segments or from one only.

(4) **"The Frozen Shoulder".** Pain of radicular distribution due to cervical spondylosis and referred to the shoulder is not infrequently followed by the condition known as "frozen shoulder" in which gross limitation of active and passive movements of the shoulder occurs and any attempt to move the joint causes pain. The possibility that a "frozen shoulder" is a symptom of cervical spondylosis should always be borne in mind.

(5) **Acute or Subacute Multiradicular Symptoms.** As a rule the radicular symptoms of cervical spondylosis are limited to one, or perhaps two, segments. The older clinical accounts of brachial neuritis, however, usually describe pain radiating down the whole length of the arm to all the digits and associated with

some degree of generalized muscular wasting, weakness, diminution of the tendon reflexes and perhaps very diffuse cutaneous sensory loss. This clinical picture may undoubtedly occur as the result of cervical spondylosis, and even when the X-ray changes are limited to one or two intervertebral joints.

Myelopathic Symptoms. The commonest early symptom of involvement of the spinal cord in cervical spondylosis is muscular weakness which is encountered with about equal frequency in one upper limb, in both upper limbs, in one lower limb, and in both lower limbs, and slightly less frequently in all four limbs. Paræsthesiæ are frequently present in one or both upper limbs. Pain is usually a radicular symptom, but painful dysæsthesiæ are sometimes experienced in the chest or in the lower limbs.

Like the symptoms, the physical signs differ in relation to the site of the disc protrusion and whether the lesion is single or multiple. The distribution of muscular wasting is variable. It may be confined to the muscles innervated by one segment of the spinal cord, or there may be moderately severe general wasting in one or both upper limbs. In some cases the wasting predominates in the hands. Exceptionally there may be generalized wasting of both upper and lower limbs. Fasciculation is often to be seen in the more actively wasting muscles. It should be noted that the site of the muscular wasting is not always to be closely correlated with the site of the compression, for, though wasting of the hands is likely to be severe when the 8th cervical and the 1st dorsal segments of the cord are compressed by a protrusion of disc C6-7, they may be almost equally severely affected when the protrusion is at a higher level, even as high as C3-4, probably as a result of interference with the blood supply to the lower segments of the cervical enlargement. As in amyotrophic lateral sclerosis, the tone of the muscles in the upper limbs depends upon a balance between the severity and the distribution of the lower motor neurone lesion and the degree of spasticity produced by interruption of descending pathways. Muscular weakness is limited to one upper limb in about one-third of the cases and present in both upper limbs in the remaining two-thirds. It is naturally the sum of the results of the upper and lower motor neurone lesions. It should be noted that the function of the pyramidal tracts may be impaired in one or two segments above the level of the cord compression in some cases. In the lower limbs the weakness is usually bilateral and of approximately equal severity. The degree of weakness present in both upper and lower limbs is usually

moderate rather than severe. There is often a complaint of weakness of the grip and clumsiness of the fingers. Most patients are able to walk, though with difficulty in the more severe cases. Sometimes a severe degree of quadriplegia develops.

The tendon reflexes in one or both upper limbs are often exaggerated. An inverted radial reflex is a valuable sign of a local lesion of the spinal cord at the 5th cervical segment. The abdominal reflexes, and the reflexes of the lower limbs, show the usual signs of a bilateral pyramidal lesion.

Cutaneous sensibility is impaired in two-thirds of all cases, the upper limbs being chiefly affected. The commonest patterns of the distribution are an impairment over one or more consecutive dermatomes in one or both upper limbs, or a limitation of the sensory loss to the hand and distal part of the forearm on one or both sides. Appreciation of passive movement is impaired in only about one-third of all cases, but may be severely affected when cutaneous sensation is well preserved. Disturbance of function of the sphincters is usually absent except in those patients in whom the cord lesion is severe. The cerebrospinal fluid is usually normal in both dynamics and composition; exceptionally either, or both, of these afford evidence of a partial blockage of the subarachnoid space.

Active and passive movements of the neck are usually relatively full and painless, but may be limited when the radicular pain is severe: in such cases passive movement of the neck may intensify the pain. Occasionally passive movement of the neck, especially extension, causes a feeling of "electric shock" to irradiate over both upper limbs and sometimes over the trunk and lower limbs as well. An exaggerated cervical lordosis, compensatory to an upper dorsal kyphosis, has been noted in middle-aged patients. It may intensify the compression of the cord by a protruded intervertebral disc.

Radiography

Radiography of the cervical spine should include lateral and anteroposterior and right and left oblique views, and it is often advantageous to take lateral views with the neck in full flexion and full extension as well as in the erect posture. In this way it may be possible to demonstrate previously unsuspected displacement of the body of one vertebra upon another. When myelography is required the best technique is to introduce 6 ml. of myodil by cisternal puncture with the patient prone and to watch the movement of the myodil on the screen. Lateral and anteroposterior films can



FIG. 9. Oblique view of cervical spine showing narrowing of intervertebral foramina C5-6 and C6-7 by osteophytes. (*The Lancet.*)



FIG. 10. Cervical spine showing, as a result of spondylosis (i) narrowing of C5-6 and C6-7 disc spaces with anterior and posterior osteophytes; (ii) spondylolisthesis, C4 slipping forward on C5 on flexion. (*The Lancet.*)



FIG. 11. Lateral myelogram showing narrowing of spinal subarachnoid space by posterior osteophytes. (*Annals of the Rheumatic Diseases.*)

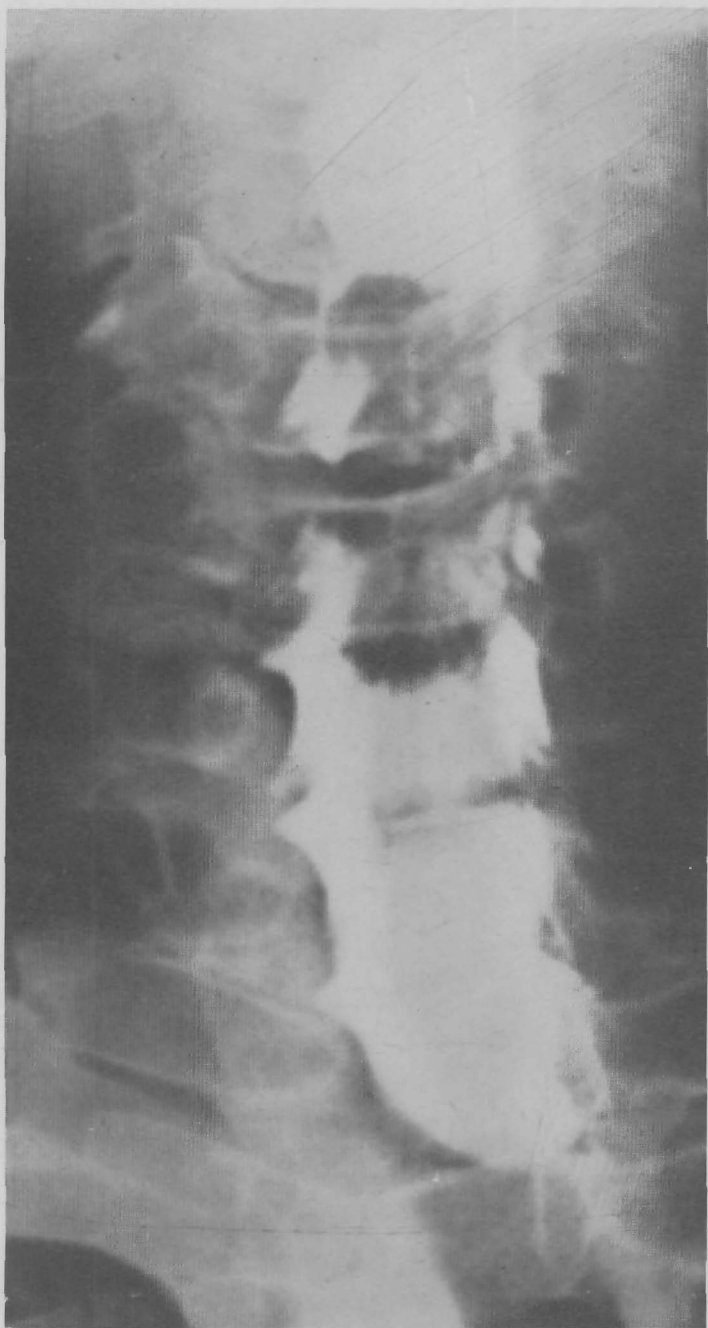


FIG. 12. Anteroposterior myelogram showing filling defect produced by disc protrusions. (*Annals of the Rheumatic Diseases.*)

be taken with the patient in the prone position, the medium being pooled in the cervical lordosis. The radiographic abnormalities which indicate a lesion of the intervertebral joints are (1) narrowing of the intervertebral disc space, (2) anterior or posterior osteophytes, (3) abnormalities in the articular surfaces of the neurocentral joints, (4) projection of osteophytes into the intervertebral foramina (Fig. 9) and (5) abnormal mobility leading to spondylolisthesis (Fig. 10). On myelography a disc protrusion leads to a filling defect, usually evident on both lateral and anteroposterior views (Figs. 11 and 12), but a small disc protrusion into an intervertebral foramen may not be easy to demonstrate on the lateral view, but may be evident as a localized filling defect obliterating one root-sleeve in the anteroposterior view. Some radiographic abnormalities in the intervertebral joints may be present without any demonstrable filling defect on myelography, especially at the C5-6 level. Conversely, a filling defect may be present without any evident abnormality on the straight X-rays, particularly at the upper cervical intervertebral joints.

Diagnosis

Three types of diagnostic problem are encountered. (1) The symptoms of cervical spondylosis may be mistaken for those of another disorder. (2) The symptoms of another disorder may be mistaken for those of cervical spondylosis because X-rays of the neck reveal the characteristic changes, which, however, in that particular case, are not responsible for the symptoms. (3) A patient may have symptoms both of cervical spondylosis and of some other disorder, neurological or otherwise.

When the symptoms of cervical spondylosis are predominantly myelopathic it may simulate disseminated sclerosis, amyotrophic lateral sclerosis, tumour of the spinal cord, syringomyelia, subacute combined degeneration, or any other condition causing progressive spastic paraplegia. The danger is that the simulation of the other disorder may be so close that it is not thought necessary to X-ray the cervical spine, the changes in which, confirmed if necessary by myelography, are necessary to establish the correct diagnosis. The radicular symptoms of cervical spondylosis may simulate a visceral disorder, such as myocardial infarction, or lesions of the brachial plexus, or peripheral nerves of the upper limbs. Conversely, since cervical spondylosis is common after middle life, and may be symptomless, there is a danger that the discovery by radiography of cervical spondylosis in a patient

suffering from some other disorder may lead to the mistaken attribution of the symptoms to the spondylosis.

Prognosis and Treatment

The natural course of the disease is to become stationary, or relatively stationary, after an initial period of deterioration. The aim of treatment therefore should be to bring about immediate improvement and facilitate the arrest of the changes in the spinal nerves and cord. Conservative treatment consists of rest in bed, immobilization of the head and neck by means of a support and physiotherapy. Traction on the head also has its advocates. The aim of operation is to relieve pressure on the spinal cord and free the cervical nerves. In some cases, particularly when there is abnormal mobility between the vertebræ, a spinal fusion may also be required. Where the lesion is producing little disability, or is restricted to one upper limb, it is probable that a period of immobilization, combined with physiotherapy, will be adequate. In patients with a short history, and particularly if there is evidence of paraplegia, operation is likely to be beneficial and the longer it is delayed the less satisfactory will be the result. In general, contra-indications to operation are a long history, severe involvement of the cord, multiple lesions, old age, and hypertension and arteriosclerosis. Brain, Northfield and Wilkinson found that about 50 per cent of patients treated conservatively showed improvement and about 75 per cent of those operated on. In 25 per cent of the latter improvement was considerable.

Immobilization of the neck usually needs to be continued for at least three months. It is usually best to begin with a plaster collar, fitting snugly to reach the occiput posteriorly and to give support to the chin anteriorly and coming up to just below the ears on either side. If the patient can move the head more than a few degrees in any direction the collar is unlikely to serve its purpose. After some weeks it may be desirable to substitute a plastic collar which the patient should, if possible, wear both by day and by night. Sometimes a felt collar is tolerated at night when a plastic one is too uncomfortable. Some form of immobilizing support to the cervical spine is usually necessary for three months.

The Effects of Injury in Cervical-Spondylosis

The mechanism of injuries of the cervical cord has recently been discussed by Taylor and Blackwood (1948) and by Barnes

(1948). When the cervical spine is previously normal, flexion injuries may cause either dislocation, crush-fracture of a vertebral body, or acute retropulsion of an intervertebral disc, while hyperextension is likely to lead to rupture of the anterior common ligament and a tear through the attachment of one of the intervertebral discs to its adjacent body. The effect of injury upon a spondylotic spine has recently been discussed by Barnes (1948), Brain, Northfield and Wilkinson (1952) and Symonds (1953). Symonds presents evidence that either a flexion injury or a hyperextension injury may be followed by a protrusion of a cervical intervertebral disc which was previously the site of degeneration. All of the authors quoted point out that severe injury to the cervical cord may occur as the result of hyperextension of the neck without the movements having caused any acute traumatic lesion of the cervical spine. The liability of the patient with cervical spondylosis to this type of spinal cord injury is probably due to a combination of factors, namely, narrowing of the spinal canal by the bosses and transverse bars, increase in the pressure of these upon the cord by hyperextension of the neck, and abnormal tension upon the cord in these circumstances owing to tethering of nerve roots in the intervertebral foramina. As Symonds points out, as a result of slow compression by cervical spondylosis the blood supply to the anterior half of the spinal cord may be so reduced that a sudden additional protrusion of a disc or stretching of the cord over a bony spur might cause immediate paraplegia and this might occur even as the result of normal movement. Symonds reports two cases of injury to the cervical spine which occurred in the course of anaesthesia for tonsillectomy and stresses the risks of movement involving hyperextension in persons already suffering from cervical spondylosis.

Such injuries of the spondylotic cervical spine may damage predominantly the spinal nerves or the spinal cord, or both, and with any degree of severity. The injury may be immediately fatal. A severe degree of damage to the cervical cord leads to considerable flaccid paralysis of both upper limbs usually with less severe impairment of power in the lower limbs. Sensation, both superficial and deep, may either be severely affected in both upper and lower limbs, or may suffer little in comparison with voluntary power. Retention of urine may occur. The patient is likely to be left with symptoms of an incomplete lesion of the cervical cord.

The most important step in diagnosis is to decide whether the

damage to the cervical cord is due to a fresh protrusion of an intervertebral disc since only in such circumstances is benefit likely to follow operation.

Examination of the cerebrospinal fluid, including Queckenstedt's test, and myelography will usually enable this point to be decided.

THE LUMBAR INTERVERTEBRAL DISC

Lumbar Spondylosis and Sciatica

Ætiology and Pathology. The distinction already drawn in the case of the cervical intervertebral disc between nuclear herniation and annular protrusion holds good also of the lumbar intervertebral disc, but the relationship between the two appears to be more complex in the lumbar spine. Acute nuclear protrusion is common and its pathogenesis is discussed below. Chronic degenerative changes in the lumbar discs, occurring in the absence of herniation of the nucleus and leading to annular protrusion, are also common. There is no doubt, however, that a small nuclear protrusion, subject perhaps, to recurrent exacerbations may lead to chronic pathological changes which are difficult to distinguish from those which result from the annular protrusion resulting from disc degeneration. Thus while the clinico-pathological picture of an acute nuclear herniation occurring in a previously normal lumbar spine is clear-cut, the clinico-pathological picture of chronic lumbar spondylosis, with or without acute exacerbation, may be the end-result of two distinct pathological processes, namely, recurrent nuclear protrusions and primary disc degeneration.

The Lumbar Discs. Bradford and Spurling (1941) discuss the physiology and the pathology of the intervertebral disc. They point out that the nucleus pulposus is incompressible, and owing to its plastic nature obeys the laws of fluids. The annulus fibrosus can be compared to a strong but somewhat elastic membrane firmly binding the vertebral bodies together. When a sudden force is put upon the intervertebral disc, the column of a fluid is displaced laterally in all directions, distending the elastic membrane. In this way not only is the shock absorbed, but the pressure is equalized over the entire intervertebral surface of each vertebra. The fluid nucleus pulposus thus acts as a shock-absorber. The annulus fibrosus must resist the pressure which tends to displace the nucleus pulposus, and in addition it binds the margins of the

vertebral bodies firmly together and thus helps to prevent excessive angulation at a single articulation.

The authors state that in about 50 per cent of all recorded cases of herniated lumbar nucleus pulposus there is a history of frank trauma, and in many other instances trauma is certainly a factor, though mild in nature. The commonest single type of injury is that due to lifting a heavy object in a bent forward position. They add that, since 75 per cent of the patients with herniation are in or beyond the fourth decade, it is apparent that the degenerative changes in the disc which begin in the prime of life predispose to herniation of the nucleus pulposus. Causal factors would include any changes in the vertebral bodies, the nucleus pulposus or the annulus fibrosus tending to limit the ability of the fluid nucleus pulposus to flow from one portion of the enclosed cavity to another or to weaken the retaining power of the annulus fibrosus. The changes in the lumbar spine associated with pregnancy are also of ætiological importance (see below).

The age-incidence shows a peak with 35 per cent of cases in the fourth decade, and between 75 and 80 per cent of all reported cases have occurred in males. It is generally agreed that 90 to 95 per cent of lumbar herniations occur at the fourth lumbar and lumbosacral discs, with a relative frequency of about two or three, but both may be affected in the same patient. A postero-lateral protrusion of the L5-S1 disc will compress the first sacral root, a postero-lateral protrusion of the L4-5 disc the fifth lumbar root and so on. A postero-lateral protrusion of a single intervertebral disc will produce uniradicular symptoms. A large protrusion more centrally placed may involve many roots of the cauda equina. The symptoms thus produced may be unilateral or bilateral.

So far we have been discussing the intrathecal compression of nerve-roots in the lumbosacral region by intervertebral disc protrusion. Whereas in the neck compression of spinal nerve roots by disc protrusion in the vertebral canal is rare compared with compression in the foramina, the reverse is generally thought to be the case at the lumbar level. Nevertheless, in the lumbar spine, exactly as in the cervical, intervertebral disc degeneration can produce damage to the spinal nerve within the foramen and in precisely the same way—first, the narrowing of the intervertebral disc narrows the corresponding foramina by bringing their edges nearer together, and, secondly, it throws an additional strain upon the articulation so leading to osteophyte formation which in

turn narrows the foramina still further. This cause of sciatic pain was hinted at by Sicard (1921) and elaborated by Putti (1927), but the subsequent discovery of intervertebral disc protrusion has led to its neglect. Lumbar foraminal pressure-radiculitis increases in frequency with age, and is most commonly encountered in the seventh and eighth decades. It is, however, especially common in diabetics, in whom it may occur at an earlier age. It may be uniradicular or multiradicular and unilateral or bilateral.

Symptomatology

Mode of Onset. Pain is almost invariably the presenting symptom and the one of which the patient chiefly complains throughout his illness. The relationship to trauma has already been discussed. The initial pain is usually situated in the lower lumbar spine and may immediately follow an injury, such as a strain in lifting or a fall, or may develop gradually after a latent period of days or even weeks. Occasionally, pain in the back and sciatic pain develop at the same time, but more frequently the pain in the leg occurs later than the pain in the back. It is not uncommon to get a history of lumbago in the past, perhaps never completely clearing up, followed by an exacerbation of the lumbar pain preceding the development of the sciatica. Or there may be a previous history both of "lumbago" and sciatica. The pain of a ruptured disc is often made worse by sitting and sometimes even by lying, so that the patient is most comfortable standing or walking about. When in bed, flexion of the affected lower limb at the hip and knee with plantar flexion at the ankle is the posture most frequently adopted. The sciatic pain is usually made worse by coughing and sneezing, and both bending the back and straightening up afterwards are likely to cause pain both in the back and in the leg. Localized numbness and paræsthesiæ are not uncommon, especially along the outer border of the foot and in the region of the external malleolus. In rare cases, pain is minimal, and the presenting symptoms may be numbness and weakness, the latter usually of dorsiflexion and eversion of the foot.

O'Connell (1944) has shown that herniation of an intervertebral disc may be the cause of sciatica or so-called lesions of the sciatic nerve which occur during labour. In such cases, pain in back or down the leg may have developed during pregnancy and be exacerbated during labour, or these symptoms may occur for the first time in the course of labour.

Sensory Examination. Sensory examination includes the search for tender areas, the performance of tests which may precipitate or exacerbate pain, and the investigation of areas of altered sensibility. The lumbosacral region should be investigated for areas of tenderness to see whether manipulation of the spinous processes or pressure just lateral to them reproduces or accentuates the patient's sciatic pain, and whether this is increased by movements of the spine. Pressure should also be exerted along the course of the sciatic nerve in the buttock and thigh to see whether the nerve trunk itself is tender. Bradford and Spurling stress the importance of the jugular compression test. Compression of both internal jugular veins for several seconds may exaggerate the pain from which the patient suffers, when pain is due to involvement of posterior nerve roots. It operates by changing the tension or position of the nerve roots by raising the pressure of cerebrospinal fluid within the spinal theca. The test is most likely to be positive among those patients whose pain is exaggerated by coughing and sneezing. Sometimes, when the pain is not evoked by the compression, it occurs when the jugular veins are released.

Lasègue's test consists of flexing the thigh to right angles with the trunk and then extending the leg upon the thigh. When the test is positive, the pain is felt either in the buttock, at the back of the thigh or behind the knee. The test may be modified by carrying it out in the usual way until slight pain is experienced, and then passively dorsiflexing the foot, or even the great toe, when the pain becomes more severe. Lasègue's test does not distinguish between pain due to lesions of the root and that caused by lesions of the trunk of the sciatic nerve. It is always positive in cases of sciatica due to herniated intervertebral disc.

Areas of altered cutaneous sensibility may be absent, but are the more often found the more carefully they are looked for. Impaired appreciation of pin-prick is most often found within the cutaneous area supplied by the first sacral segment; this includes approximately the outer half of the dorsal and plantar aspects of the foot, including the three outer toes, and the outer aspect of the lower one-third of the leg together with a small area in the buttock. The analgesic area may ascend into the second sacral cutaneous distribution and then involve the posterior surface of the leg and thigh. Occasionally, all the sacral cutaneous segmental areas are affected. When the fifth lumbar area is affected, the two inner toes and the inner aspect of the foot will be analgesic. The fourth lumbar area will be involved only when the herniation occurs

between the 3rd and 4th lumbar vertebræ, and the analgesic area will then extend from below the internal malleolus up the inner aspect of the leg as far as the knee. Hyperalgesia of one or more cutaneous segmental areas is less commonly found.

Motor Symptoms. There is usually slight wasting and hypotonia of the glutei, hamstrings and all muscles below the knee. Actual muscular weakness may be slight or absent; if present to any marked degree, it is usually found in the muscles which dorsiflex and evert the ankle and those which dorsiflex the toes. Weakness of plantar flexion of the ankles and toes may also be present.

Reflex Changes. Diminution or loss of the ankle-jerk on the affected side is the most constant sign of a herniated lumbar intervertebral disc. The knee-jerks are usually normal, but there may be some depression of the knee-jerk on the affected side when the herniation occurs between the 4th and 5th lumbar vertebræ. If either sensory loss or motor weakness is severe, the plantar reflex on the affected side may be diminished.

In *intraforaminal pressure radiculitis* pain is usually less severe than in sciatica resulting from disc protrusion and is less likely to be exacerbated by coughing or sneezing. It is often, however, influenced by posture and may be worse when the patient is sitting. There may be no pain, but only dysæsthesiæ in the distribution of the dermatomes supplied by the affected root or roots. Cutaneous sensibility is often blunted over these areas. When several roots are involved there may be conspicuous muscular weakness and wasting associated with fasciculation, and diminution or loss of the knee jerks.

The Spine. Some rigidity of the lumbar muscles is commonly present, and the normal lumbar curve may be obliterated or reversed. Lumbar scoliosis is common: the convexity of the spine may be either towards or away from the side of the sciatic pain, or may alternate from side to side. Usually the convexity is away from the side of the pain, with tilting of the pelvis so that the affected hip is held higher than the normal one. Pain is most likely to occur on forward bending and on deviation away from the side of the lesion.

X-ray Examination. X-rays of the lumbosacral spine should be carried out in all cases of sciatica, since many causes of sciatic pain are associated with bony changes visible in radiograms. These include congenital abnormalities, spondylosis, spondylolisthesis, injuries, neoplasms and infections of the spine and sacroiliac joints. Narrowing of the disc-space might be expected to be



FIG. 13. Protrusion of the disc between the fifth lumbar body and the upper part of the sacrum causing a reduction of the intervertebral disc space.

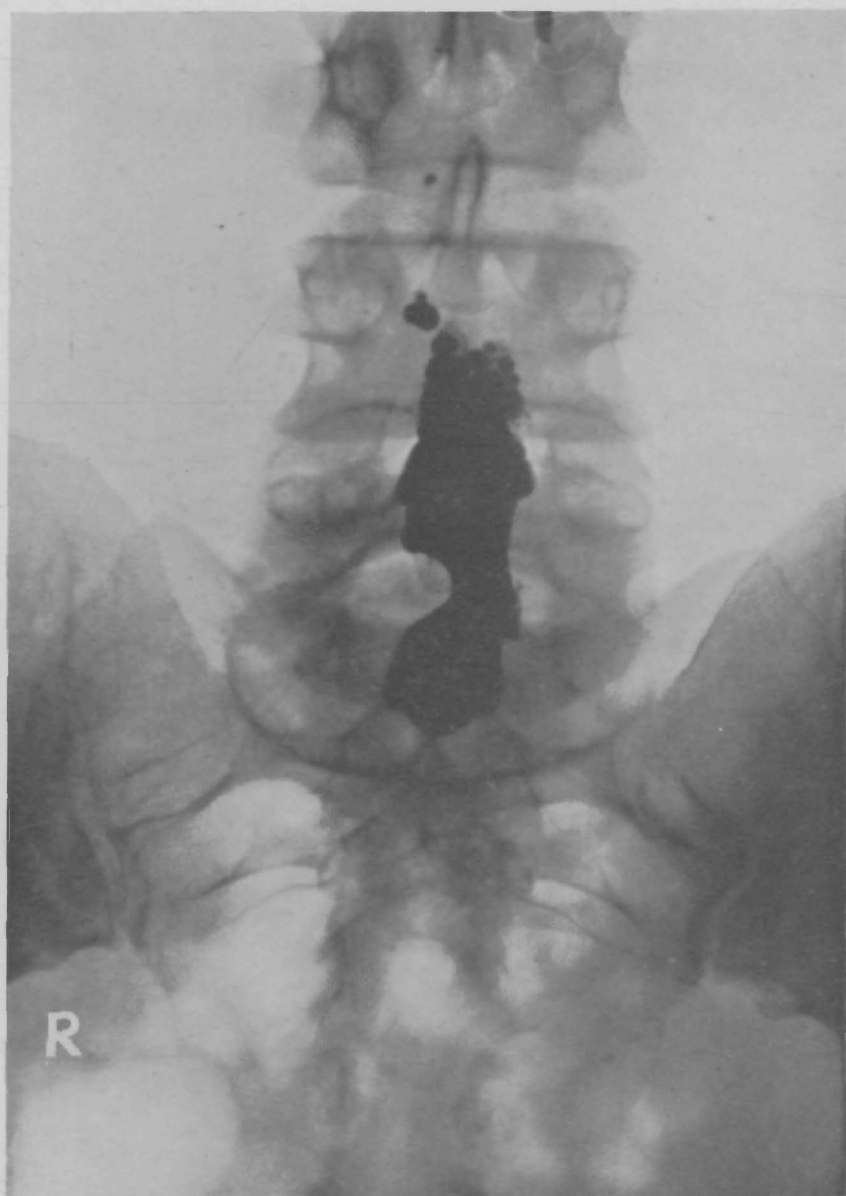


FIG. 14. Protrusion of the disc on the right side between the upper part of the sacrum and fifth lumbar vertebra, shown by a defect in the column of intrathecal lipiodol. The shadow of the nerve-root on the right is obliterated, while that on the left and those of the segment above are seen. (Figs. 13 and 14 kindly lent by Dr. M. Jupe.)

significant (Fig. 13) but the lumbrosacral disc is often normally narrower than the other lumbar discs, so experience is required to estimate the significance of reduction in the thickness of the disc. Narrowing of the fourth lumbar disc is significant, especially if associated with sclerosis of the adjacent vertebral bodies or local spondylosis. Foraminal compression will be associated with narrowing of the foramen by osteophytes.

Myelography. Radiography after the injection of myodil is not necessary in every case, as it is often possible to be sufficiently certain of the diagnosis and localization of a herniated intervertebral disc after clinical examination, investigation of the cerebrospinal fluid and plain radiography. Myelography, therefore, should be reserved for doubtful cases. For the actual technique of myelography, readers are referred to Bradford and Spurling's book. The essence of the procedure is that, with the patient on a screening table which can be tilted, the myodil is made to flow slowly over each interspace in order to detect a filling effect which is confirmed by repeating the tilting from either direction. Antero-posterior and lateral films are made of any region suspected of being abnormal.

Bradford and Spurling stress the importance of expert interpretation of the examination, since, on the one hand, very slight abnormalities may be the only radiographic evidence of a definite herniation of the nucleus pulposus, while, on the other hand, obvious irregularities in the myodil column may indicate nothing abnormal, since posterior protrusion of the intervertebral disc within normal limits may indent the anterior dura sufficiently to affect the flow of myodil decidedly. The most characteristic sign of a herniated intervertebral disc is a unilateral filling defect without indentation of the opposite side (Fig. 14). Such a defect always overlies the intervertebral disc in part, though the major portion of the herniated material may slip over the body of the vertebra. A mid-line filling defect is unusual but indicates a herniation, part of which is in the middle line.

Myelography with air will frequently demonstrate a herniated intervertebral disc, but the method is not so reliable as radiography with myodil. When air is used, it should be introduced in excess of the amount of cerebrospinal fluid removed in order to distend the dural sac.

The Cerebrospinal Fluid. Lumbar puncture for diagnostic purposes in suspected cases of herniated disc should be carried out if possible between the fifth lumbar and the first sacral laminae in order to be below a partial or complete block if such exists. A

block is present, however, in only a very small percentage of lumbar herniations. The characteristic abnormality of the cerebrospinal fluid is a rise in the protein content due to venous congestion of the nerve root or roots compressed by the herniated nucleus pulposus. A raised protein content of the fluid occurs in about 80 per cent of cases so that a normal cerebrospinal fluid does not exclude a herniated disc. The average figure for the protein content is between 60 and 90 mgm. per cent. An increase in the cell count is unusual and should suggest some other cause.

Diagnosis

Herniated lumbar intervertebral discs have to be diagnosed from the numerous other conditions which may cause pain of sciatic distribution. Neoplasm of the cauda equina causes symptoms which are usually insidious in onset and signs which are commonly more extensive than those of herniated intervertebral disc, and usually bilateral. Sphincter involvement often occurs in the later stages. There is more likely to be a block of the spinal subarachnoid space, and the protein content of the cerebrospinal fluid is usually considerably raised. The symptoms of compression of the roots of the sciatic nerve by secondary neoplasm are also usually insidious in their onset and steadily progressive. There is usually a history of the primary neoplasm or evidence of its presence, and the patient's general condition is likely to be somewhat cachectic. X-rays of the lumbosacral region may show characteristic bone-destruction. Lumbar spondylosis is sometimes associated with symptoms of radiculitis. In such cases, muscular wasting and sensory loss are usually found on the anterior aspect of the thigh as well as below the knee, and the X-ray changes are characteristic. Spinal injury, spondylolisthesis and congenital abnormalities of the lumbosacral spine are all demonstrable by radiography. Congenital abnormalities may certainly be responsible for low-back pain, but it is doubtful whether in themselves they can cause sciatica. Spinal injury, of course, may be associated with a herniated intervertebral disc. The importance of fibrositis as a cause of referred pain has been stressed by Kellgren (1941). The diagnosis rests upon the presence of tender spots in a muscle, usually in the case of sciatica one of the glutei, with pain, referred to the periphery of the limb, which can be abolished by injection of the tender spot with a few c.c. of 2 per cent procaine hydrochloride. There is no doubt that such cases occur, though it is rarely that fibrositis gives rise to pain which in severity and distribution resembles that caused by

a herniated intervertebral disc, and it should be remembered that positive evidence of a nervous lesion excludes fibrositis. Observations by Elliott (1944) show that a root lesion may cause symptoms similar to those hitherto regarded as pathognomonic of fibrositis. He describes a form of myalgia, arising in muscles supplied by an irritated root, which simulates fibrositis both clinically and in its response to local injections of procaine. Relief from procaine does not therefore exclude a root lesion. Elliott's electromyographic studies show that the tender spots in the muscle were as a rule the seat of a localized increase in irritability and a continuous discharge of action-potentials.

It remains to consider the diagnosis between a herniated intervertebral disc and sciatic neuritis. The difficulties of the diagnosis and the controversy over the relative frequency of these two causes of sciatica have been discussed by Symonds (1943). After stressing the absence of pathological evidence for the existence of sciatic neuritis, he concludes that there is "no clinical variant of the syndrome under discussion (sciatica with signs of nervous lesion), which has not been proved in many cases to be associated with compression of an appropriate nerve root by a prolapsed disc; and that when the pain before operation has been severe, immediate post-operative relief is the rule." The fact that most surgeons have recorded cases in which, although the clinical picture has been indistinguishable from that of a proved disc lesion, no such lesion has been found on operation may be explained by faulty observation or possibly by the absence of protrusion of the disc with the patient in the prone position in operation. Recovery from pain without operation has been held to favour sciatic neuritis, but it is possible that disc protrusion may be displaced so that it no longer compresses a nerve root or that if there is only a bulge of the annulus this may recede when the intra-annular pressure is reduced by the horizontal posture and in time the annulus may be repaired.

It is generally agreed that in the past most patients with sciatica which would now be attributed to a herniated intervertebral disc did in fact recover without operation. The correlation between the presence of a herniated disc and sciatica on the one hand and the removal of the disc and the relief of pain on the other seems to leave no doubt that a herniated disc is a relatively frequent cause of sciatica and therefore that recovery without operation is not an argument in favour of sciatic neuritis as against herniated disc. It must be admitted that in many cases it is impossible on clinical

grounds to distinguish between sciatic neuritis and a herniated intervertebral disc. Sciatic neuritis is favoured by physical signs indicating involvement of the whole sciatic nerve in its motor and sensory functions as opposed to the signs of damage to a single root or possibly two roots which are compressed by a herniated disc, especially when muscular wasting and weakness are conspicuous in a number of the muscles innervated by the sciatic nerve. A leucocytosis in the cerebrospinal fluid favours sciatic radiculitis rather than root compression.

Treatment

As already stated, past experience has shown that most patients with a herniated intervertebral disc recover completely if treated conservatively. Operation should therefore be reserved for those whose symptoms do not respond to other measures and become chronic, those who relapse, and those with gross and persistent signs of root compression sufficiently severe to cause disability.

Conservative treatment consists primarily of rest in bed, to which are added various measures designed to immobilize the lower part of the spine and the affected lower limb. These include a long Liston's splint or a plaster jacket, and the injection of saline into the sacral epidural space. This sometimes gives dramatic immediate and lasting relief, but in other cases it is disappointingly ineffective. It presumably operates by shifting a nerve root from the point of pressure by a prolapsed disc. When rest in bed for several weeks has been tried and failed, immediate relief is sometimes given by the application of a plaster jacket which fixes the lumbar spine in slight extension. The patient, who is allowed to walk about, should wear the plaster for three months. Physical therapy in its various forms is merely palliative, but graduated exercises are of value when the pain has gone.

The results of operation are reviewed by Bradford and Spurling who conclude that good results are obtained in 90 per cent or more of cases of herniation of intervertebral disc in the lumbar region, with a surgical mortality of 1 per cent or less. In their own series of 166 verified cases, four patients had to be re-operated upon for a recurrence, and in four other cases recurrence was suspected. Whenever extensive laceration of the annulus fibrosus is found, they recommend that the patient should be fitted with a low backbrace. O'Connell (1951) reviews the results of operation in 500 cases. In 92 per cent pain was either completely removed or greatly diminished and only 1 per cent were not improved at all.

A second operation was required in 10 per cent. Burns and Young (1951) report a series of 913 patients operated upon, of whom 616 with a disc protrusion were followed up. The results were as follows:—

No pain or disability	56·6 per cent
Occasional pain	15·9 per cent
Improved	20·3 per cent
Failures	7·2 per cent

Half of the patients whose operation was a failure were re-explored. In nine out of the 22 another protrusion was found at operation. There is no general agreement as to whether, or in what cases, spinal fusion should be carried out in addition to removal of the disc protrusion.

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CHAPTER 10

THE CEREBRAL CIRCULATION

Anatomy and Physiology

CEREBRAL angiography has literally thrown new light upon the cerebral circulation. Not only have we learned to study what happens to an opaque substance injected into the internal carotid or vertebral artery in various circumstances, but the discovery by means of angiography of the effects upon the cerebral circulation as a whole of obstruction of one of the main vessels has aroused fresh interest in the normal regulation of the blood flow through the brain.

McDonald and Potter (1951) have made an experimental study of this in the rabbit, in which animal the disposition of the cerebral arteries is similar to that seen in man. Their observations showed that the internal carotid artery and the vertebral artery share the blood supply to their own half of the brain in such a way that there is normally no interchange of blood between them. The opposing streams of the carotid and vertebral arteries meet in the posterior communicating artery at a "dead point", at which the pressure of the two is equal, but do not mix there. If, however, both internal carotids or both vertebral arteries are occluded, blood passes forwards or backwards respectively from the pair which are still patent. There is then a functioning anteroposterior anastomosis in each posterior communicating artery. Occlusion of one internal carotid or one vertebral artery results in the supply by the contralateral fellow of the territory which would otherwise be deprived of blood. There is therefore also a side to side anastomosis. Normally, however, the vertebral artery supplies its own side of the spinal cord and contributes a strictly unilateral stream to the basilar artery, for it is stated that the two streams from the vertebral arteries remain each on its own side of the basilar and do not mix. Consequently the blood from each vertebral artery is distributed ipsilaterally to the brain stem, cerebellum, posterior cerebral artery and as far as the caudal part of the posterior communicating artery territory.

Schmidt (1950) has published a monograph on the "Cerebral Circulation in Health and Disease". Schmidt states that the

present state of our knowledge supports the view that the cerebral circulation normally tends to follow passively upon changes in arterial pressure to a greater extent than is the case in most other organs, but it probably has greater capacities for resisting or compensating for such changes than had been suspected. Although constriction of cerebral blood vessels has been demonstrated as the result of stimulation of sympathetic nerves, the significance of this finding is by no means clear and in Schmidt's view the signs of cerebral vasoconstriction revealed by direct instrumentation of the cerebral cortex in the cat or rabbit should be regarded as a vestigial remnant of an undesirable type of control rather than as an expression of a physiologically useful and important mechanism. The available evidence indicates that the extracranial parts of the cephalic circulation are much more markedly influenced than the intracranial by impulses carried by the cervical sympathetic nerves. In view of the fact that beneficial effects have been reported from unilateral block of the stellate ganglion in patients showing symptoms of cerebral thrombosis it should be noted that, according to Schmidt, even bilateral stellate block does not significantly affect cerebral blood flow or cerebral vascular resistance in normal or in hypertensive individuals. Although there is also evidence of a vasodilator cerebral innervation, the functional significance of this is at present wholly unknown.

The cerebral vessels, however, are dilated by all of the usual products of metabolism (decreased oxygen, increased carbon dioxide, increased acidity and increased temperature) as well as a number of other agents which have recently come to be associated with cellular activity. The cerebral vessels are also constricted by some of the reverse changes, especially by increased oxygen and decreased carbon dioxide. The available evidence in fact shows that the behaviour of the cerebral circulation under physiological as well pathological conditions is influenced more by agents of this kind than by any other factor, and Schmidt concludes that CO_2 tension is a dominant influence in regulating both the tone of the cerebral blood vessels and the activity of the respiratory centre over the ordinary physiological range. The cerebral vessels appear to be even less susceptible to the various classes of vasoconstrictor drugs than to the vasodilators. Schmidt observed that while the sympathomimetic vasoconstrictor agents (epinephrine, benzedrine, ephedrine, etc.) apparently are capable of constricting cerebral vessels in monkeys (and presumably in man) if the concentration acting here is made higher than it is elsewhere it is doubtful if this

has any practical value. However he points out that the considerable differences between the effects in cats and in monkeys should suggest caution in applying these findings to man and it is possible that human cerebral vessels are as superior to the monkeys in reactivity to vasoconstrictors as the monkeys are to the cat. There is, however, evidence that the cerebral vessels undergo just as intense constriction in essential hypertension in man as those elsewhere in the body.

Schmidt reviews observations on the cerebral blood flow in man, particularly a number of observations by Kety. These demonstrated that inhalation of air with an increased CO_2 content produced the highest cerebral blood flow encountered in any condition except organic cerebral arteriovenous communication. The cerebral vascular resistance was also reduced to a low level, thus supporting the belief that CO_2 has a relatively specific vasodilator effect on cerebral blood vessels. In patients with simple hypertension the cerebral blood flow, oxygen consumption and arteriovenous oxygen difference were all normal. This was brought about by a concomitant increase in cerebral vascular resistance equal to the elevation in mean blood pressure which is taken to mean that the cerebral vessels participate equally with the vessels in the body as a whole in the increased tonus which characterizes hypertension. In a group of six patients with hypertension and distinct sclerosis of palpable arteries associated with mental deterioration, which was held to indicate the presence of cerebral arteriosclerosis, the cerebral blood flow and oxygen consumption were definitely sub-normal and similar observations were made in patients suffering from senile dementia without hypertension or obvious arteriosclerosis.

The Relative Frequency and Age Incidence of Cerebral Vascular Disorders

The frequency of cerebral vascular disorders as a cause of death is increasing. According to the figures of the Registrar General for England and Wales the number of persons who died from these causes in 1942 was 56,048 and in 1952 59,388. The latter figure constituted approximately 14 per cent of the total deaths.

Fig. 15 shows the age distribution of cerebral vascular disorders in 200 cases, 100 of which were seen in hospital and 100 in private consultation. It will be noted that more than one-third of the cases occur below the age of fifty. Fig. 16 shows the difference

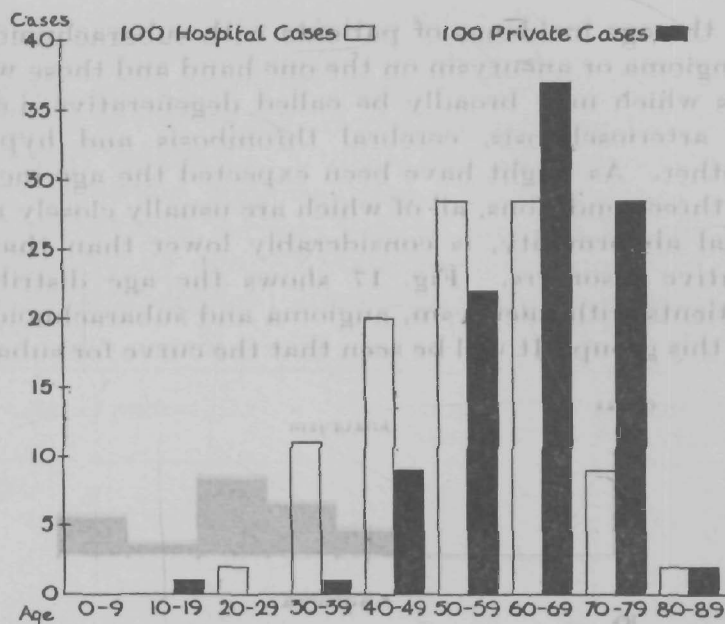


FIG. 15. Cerebral vascular disease. Age incidence in 200 cases.

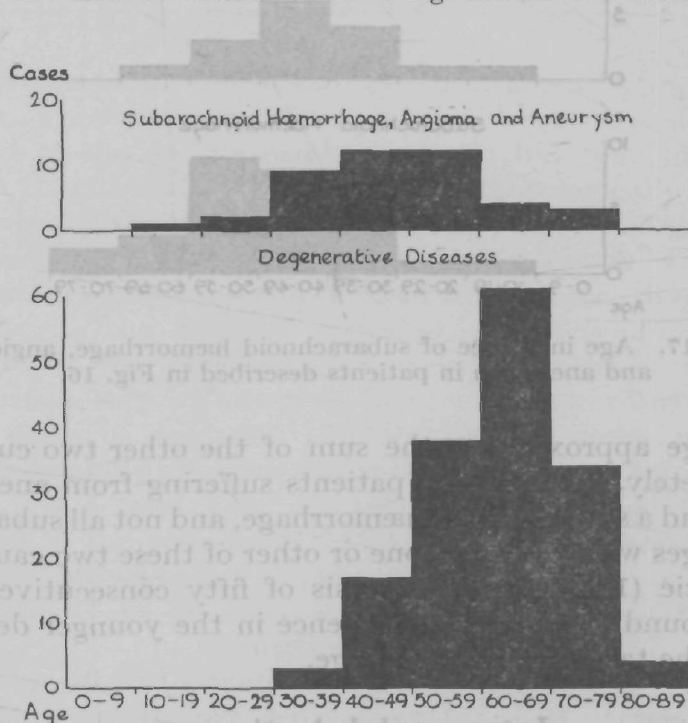


FIG. 16. Cerebral vascular disease. Age incidence of subarachnoid haemorrhage, angioma and aneurysm compared with age incidence of other degenerative diseases. (200 cases)

between the age incidence of patients with subarachnoid hæmorrhage, angioma or aneurysm on the one hand and those with other disorders which may broadly be called degenerative, i.e., chiefly cerebral arteriosclerosis, cerebral thrombosis and hypertension on the other. As might have been expected the age incidence of the first three conditions, all of which are usually closely related to congenital abnormality, is considerably lower than that for the degenerative disorders. Fig. 17 shows the age distribution of those patients with aneurysm, angioma and subarachnoid hæmorrhage in this group. It will be seen that the curve for subarachnoid

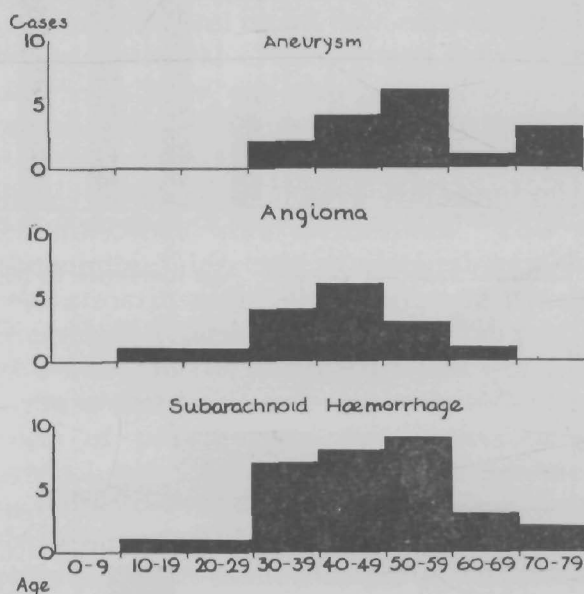


FIG. 17. Age incidence of subarachnoid hæmorrhage, angioma and aneurysm in patients described in Fig. 16.

hæmorrhage approximates the sum of the other two curves, but not completely, since not all patients suffering from aneurysm or angioma had a subarachnoid hæmorrhage, and not all subarachnoid hæmorrhages were traced to one or other of these two causes.

Mackenzie (1953) in his analysis of fifty consecutive cases of angioma found a higher age-incidence in the younger decades, as shown in the table on opposite page.

Intracranial Angiomas

Cerebral angiography has greatly increased our knowledge of the incidence and symptomatology of intracranial vascular

abnormalities, a subject which was fully discussed at the Fifth International Neurological Congress (1953).

Pathology. Angiomas were originally divided by Cushing and Bailey (1928) into venous and arterial varieties, but this distinction is now generally regarded as artificial and the angiomas are looked upon as arteriovenous malformations. They consist of a mass of enlarged and tortuous cortical vessels, supplied by one or more large arteries usually derived from the blood supply of one, but sometimes of both, cerebral hemispheres, and sometimes fed also

<i>Age of patient</i>	<i>At onset of symptoms</i>	<i>At time of diagnosis</i>
1-10	5	0
11-20	24	10
21-30	6	13
31-40	9	8
41-50	5	12
51-60	1	7

from below the tentorium, and they are drained by one or more large veins. These malformations are most frequently encountered in the field of the middle cerebral artery, but may involve the brain-stem (Logue and Monckton, 1954). Histologically degeneration of cerebral tissue with gliosis is observed between the vessels.

Frequency and Age-Incidence. Mackenzie (1953) has recently reviewed 50 consecutive cases of angioma, diagnosed by angiography, in the National Hospital, Queen Square, between 1946 and 1951. In a series of 200 consecutive cases of cerebral vascular disease seen by one of us there were 13 verified and three suspected cases of angioma. In Mackenzie's series males and females were equally affected: 10 per cent complained of symptoms during the first decade of life and two of these had a subarachnoid hæmorrhage at the age of ten. Two-thirds of the remainder had their first symptoms before the age of 30.

Symptomatology

Angiomas of the Cerebral Hemispheres. In Mackenzie's series of patients 16 per cent presented with epilepsy which appeared in the youngest at 11 and in the oldest at 42. Nine had attacks which were focal in onset and in all except one the attacks

displayed at some time or other focal features. The attacks were found to show variability in individual patients as well as in themselves, and, whether focal or generalized, a widely varying periodicity. Some patients whose initial attacks were focal had long periods of remission.

In 15 cases the presenting incidence was a hæmorrhage, usually in part subarachnoid, but in three cases apparently purely intracerebral. Of the 12 patients presenting with subarachnoid hæmorrhage the youngest was 15 and the oldest 45. In most cases there was nothing remarkable about the history. Five of these had no abnormal physical signs. Three subsequently developed epilepsy, two within a few months of the hæmorrhage. Thirteen years was the longest period in Mackenzie's series between a single proven incident of hæmorrhage and the diagnosis of an angioma.

In 12 patients the first symptom was headache which was sufficiently severe to constitute a genuine disability. With one exception it was a symptom which appeared early, and often exhibited a periodicity. In seven patients the episodes in which periodic headache was the prominent symptom had for their onset migrainous features. It was usually possible to recognize, however, that the migraine was in some ways atypical. Whereas in migraine the sensory symptoms tend to alternate from one side of the body to the other, in a patient with an angioma these symptoms, if not bilateral, as is sometimes the case, occurred persistently on the same side and the headache again, if not generalized, was persistently one-sided and on the side of the angioma. A persistent homonymous visual field defect should also suggest the presence of an angioma.

Of the remaining seven patients of MacKenzie's series of 50, six were first aware of weakness of a limb or limbs. Finally, there was one patient who complained first of proptosis.

Mackenzie points out that not only the presenting symptom, but even more the pattern produced by additional symptoms, suggests the diagnosis of cerebral angioma. Thus, four patients presenting with epilepsy subsequently had a subarachnoid hæmorrhage; five presenting with hæmorrhage subsequently developed epilepsy, and five out of seven patients with atypical migraine. Of six presenting with hemiparesis, two had repeated subarachnoid hæmorrhage and three developed epilepsy.

Thirty-five patients, or 70 per cent, had abnormal signs in the nervous system. Eleven out of 16 patients presenting with epilepsy had hemiparesis of some degree, but in none was there any defect

in the visual fields. Five out of 12 patients presenting with subarachnoid hæmorrhage had permanent abnormal signs in the nervous system, in four of whom the visual fields were to some extent involved, this being in two the only defect.

An audible bruit was present in 23 of 34 patients when the presenting symptom was other than a hæmorrhage, but in only one of 14 patients in whom hæmorrhage was the initial occurrence. As might have been expected, there was a correlation between the situation of the angioma and the symptoms presented. Thus paracentral angiomas tend to present with epilepsy. Angiomas presenting with hæmorrhage tend to be more deeply placed in the hemispheres than those presenting with epilepsy, while parieto-occipital angiomas are most likely to simulate migraine.

Angiomas in the Posterior Fossa. Logue and Monckton (1954) have recently reported nine cases of angioma in the posterior fossa. In two cases the angioma was limited to the cerebellum and in the remainder it predominantly involved the brain-stem, but sometimes extended to involve the cerebellum. The clinical presentation of cerebellar angioma was that of cerebellar apoplexy with mild 6th nerve involvement and scattered pyramidal tract signs. The seven patients with brain-stem angiomas presented in three different ways. In four the initial disturbance was subarachnoid hæmorrhage, in two there were signs of progressive neurological disablement extending over 15 years and in one case there was acute obstructive hydrocephalus. The general neurological picture was that of a progressive disorder, sometimes fluctuating or intermittent, of the 3rd to the 11th cranial nerves, with, in the limbs, symptoms of pyramidal tract involvement or cerebellar ataxia or tremor. Four of these seven patients had subarachnoid hæmorrhage and three had a cranial bruit. The authors stress these points in relation to diagnosis. When the initial symptom is subarachnoid hæmorrhage and there are no signs of involvement of the brain-stem the diagnosis can only be made by vertebral angiography, probably after carotid angiography has failed to disclose a source for the bleeding. When the signs are those of an intermittently progressive brain-stem lesion they may suggest disseminated sclerosis. The persistently localized character of the lesions, however, may cast doubt on this. Finally, cases which follow a steadily progressive course can only be distinguished from a brain-stem glioma by means of vertebral angiography.

The value of angiography in the diagnosis of angiomas occurring

both above and below the tentorium is discussed elsewhere in this book (see pp. 257-261).

Treatment

The ideal treatment of a cerebral angioma is surgical removal. In the past the majority of these abnormalities have been inoperable on account of the difficulty of controlling hæmorrhage. The successful removal of even a small angioma may prove life-saving by preventing intracerebral or subarachnoid hæmorrhage. Olivecrona (1953) reports the removal of 60 angiomas in 96 cases. The mortality rate was 11·7 per cent and 37 of the 53 survivors were well and able to work. The use of hypotensive drugs may increase the number of angiomas which it is possible to remove. The effects of radiotherapy are uncertain: occasionally improvement in symptoms seems to occur as a result.

Thrombosis of the Internal Carotid Artery

We owe to cerebral angiography the recognition of the syndrome of thrombosis of the internal carotid artery which was first described by Moniz, Lima and de Lacerda (1937). Angiography by establishing the diagnosis during life has drawn attention to the clinical picture, which is still being expanded by clinical observation.

Although for convenience we have spoken of thrombosis of the internal carotid artery, the same problem of terminology arises here as in the case of cerebral thrombosis generally, namely, that it is often impossible to be certain clinically that the symptoms of cerebral infarction are always the result of obstruction of an artery by thrombus. In other words, impairment of cerebral function may occur intermittently or persistently as the result of defective blood supply caused by narrowing of an artery, for example, by atheroma, before actual thrombosis has occurred.

Pathology. The subject has recently been reviewed by Cloake (1951). Hultquist (1942) found 69 cases in 3,500 necropsies and thought that all were due to arteriosclerosis. Cloake favours the view that in some cases at least the lesion is that of thrombo-angiitis obliterans. In general it appears that thrombosis of the internal carotid artery may be caused either by atheroma or by thrombo-angiitis obliterans and probably in most cases the former is the cause. It commonly occurs during the 5th and 6th decades

of life and in five out of six cases in men. The commonest site of thrombosis is just above the bifurcation of the common carotid, less frequently it occurs inside the syphon within the skull.

The fact that thrombosis of the internal carotid artery is sometimes discovered on angiography, without the patient's having had any symptoms which could be referred to the lesion, illustrates the importance in relation to the production of symptoms of the state of the circulation in the circle of Willis and in the branches of the internal carotid artery. Here we enter territory which is still largely unexplored. A number of factors may influence the cerebral circulation after occlusion of the internal carotid artery. These include the condition of the remaining cerebral arteries, including particularly the rest of the circle of Willis, through which, as shown above, a collateral supply will normally be established, the occurrence of spasm in the remainder of the internal carotid artery, and possibly its branches, the extension of thrombosis from one to the other or possibly, before occlusion is complete, the detachment of emboli from the internal carotid and their carriage into its branches. Metabolic factors at the time may also influence the behaviour of the cerebral circulation.

Symptomatology. As stated above, thrombosis of the internal carotid artery can occur without producing any symptoms whatever. This, however, is exceptional. Probably there are prodromal symptoms which may extend over a period of a year or more. Characteristically these are transitory disturbances presumably due to attacks of ischæmia occurring within the territory of supply of the affected internal carotid. Such symptoms, therefore, may be very varied and may include transitory attacks of amblyopia in the eye on the affected side, of mental confusion, of aphasia and of weakness or dysæsthesiæ on the opposite side of the body. Focal motor or sensory epileptiform attacks, or even generalized epilepsy, may occur. It is probably possible for complete occlusion of the internal carotid to take place without any further disturbance, in which case the prodromal symptoms may disappear or continue. More often, however, complete occlusion of the vessel leads to a more lasting disturbance of function of the affected cerebral hemisphere. This varies in severity from a slight contralateral hemiparesis, with or without sensory loss, to complete hemiplegia with sensory loss and sometimes crossed homonymous hemianopia, and, when the left hemisphere is involved, mental confusion and expressive and receptive aphasia. With the more severe lesions consciousness may be lost.

The degree of recovery of function is equally variable and no doubt depends upon how far it is possible for a collateral circulation to be established through the circle of Willis before irreparable damage has been done. When the symptoms are relatively slight, recovery may be complete or almost so, and a substantial degree of recovery even from hemiplegia may occur after a few weeks. When aphasia is present, some residual difficulty with speech is common and there is often some permanent impairment of the higher mental functions, including control over the expression of emotion. At the worst, all the functions of that part of the hemisphere which receives its blood supply from the internal carotid may be permanently lost. When substantial recovery is going to occur, it usually begins within a week of the onset of symptoms of occlusion. Amblyopia is very rarely permanent.

As in the case of arteriosclerotic lesions generally, thrombosis of the internal carotid artery may, or may not, be associated with hypertension. It is often possible to demonstrate diminution of the internal carotid pulse on the affected side, but this is not always easy and a failure to detect any difference does not exclude the possibility of a thrombosis. In cases of doubt, and when it is necessary to establish the diagnosis, in order to exclude a lesion of some other kind this can be done by angiography (see p. 259).

Treatment. There is no established advance in treatment of this lesion to be recorded. The value of cervical sympathetic block is not proven. Anticoagulants are being employed, but their value has also yet to be assessed. The first necessity is clearly to be certain of the diagnosis. It has been suggested that there may be some danger in the use of anticoagulants owing to the risk of hæmorrhage from an infarcted area, but Wright and McDevitt (1954) point out that this danger has not been encountered in the use of anticoagulants in the treatment of coronary thrombosis. It is possible that anticoagulants may prove useful for two purposes, namely, to prevent, or postpone, actual thrombosis when prodromal symptoms indicate atheroma of the artery and, when thrombosis has actually occurred, to diminish the likelihood of its occurrence in the cerebral arteries.

The Treatment of Subarachnoid Hæmorrhage

The clinical picture of subarachnoid hæmorrhage is now generally recognized and is readily confirmed by lumbar puncture. Most patients who come under observation suffering from subarachnoid hæmorrhage have not had a previous diagnosis of the

cause. This, therefore, should be the next step. Bleeding into the subarachnoid space may be arterial, capillary or venous, and its site of origin single or multiple. A head injury is not likely to give rise to difficulty in diagnosis. Hæmorrhage resulting from capillary damage may be present in exceptionally acute forms of encephalitis or encephalopathy. In such cases, however, the blood is never present in such large amounts as occur when the hæmorrhage comes from rupture of a large vessel and the symptoms and signs of multiple or diffuse lesions within the nervous system are usually much more prominent than those of the subarachnoid hæmorrhage. Subarachnoid hæmorrhage may occur as a symptom of hæmorrhagic diseases, especially thrombocytopenic purpura. It is uncommon for it to be the presenting symptom of such diseases however, and the diagnosis is usually established through observation of other hæmorrhagic lesions and examination of the blood. Alpers and Gaskill (1944) state that subarachnoid hæmorrhage from a vein may occur in pyæmic states. Here again the cause is usually obvious. Intracerebral hæmorrhage, due to vascular degeneration associated with high blood pressure, may reach the subarachnoid space either by rupture into the ventricular system or, more rarely, through the surface of the brain. In such cases the presence of hypertension, and the prominence of the signs of the original destructive lesion of the brain, usually make the diagnosis easy. Confusion is likely to arise only in the case of a hypertensive patient who has bled both into the substance of the brain and into the subarachnoid space from an intracranial angioma. Spontaneous spinal subarachnoid hæmorrhage usually comes from angioma of the spinal cord. The earliest symptoms of such a disorder are pain in the spine accompanied by spinal rigidity and referred to the lower limbs, which may show muscular weakness and loss of tendon reflexes, and there is likely to be disturbance of bladder function. Cerebral symptoms develop later.

The two remaining causes of subarachnoid hæmorrhage are the principal ones, namely, intracranial aneurysm and intracranial angioma. Hæmorrhage from an intracranial aneurysm usually occurs in the subarachnoid space: less frequently the substance of the brain is also invaded. Nevertheless intracerebral rupture is not a rare occurrence, as Robertson (1949) found 56 instances in 93 post mortems. The incidence in all cases, however, must be considerably lower than this, for intracerebral hæmorrhage would naturally contribute to a fatal result. A patient suffering

from cerebral angioma, however, usually presents with some symptoms other than subarachnoid hæmorrhage. Thus in MacKenzie's (1953) series of 50 cases only 30 per cent presented with hæmorrhage, which was subarachnoid in 24 per cent.

In dealing with a case of subarachnoid hæmorrhage the first question to be considered is whether it is caused by a lesion which is likely to be amenable to surgical treatment. Blood diseases are rare causes but should be borne in mind, and if the patient has hypertension and shows signs of an intracerebral as well as a subarachnoid hæmorrhage the cause is probably rupture of an atheromatous vessel. This is not certain, however, since a patient with hypertension may have an intracranial aneurysm or even an angioma. Hæmorrhage associated with blood disease or from an atheromatous vessel is not often amenable to surgery.

In order to determine whether the cause is an aneurysm or an angioma it is necessary to perform angiography. When the physical signs suggest that the lesion is on one side carotid angiography should first be performed on that side, and then, if necessary, on the other. If both yield negative results the possibility that the hæmorrhage comes from the posterior fossa should lead to the consideration of vertebral angiography. In most cases of aneurysm or angioma carotid angiography will reveal the lesion (see chapter 13, p. 259), but in some cases when the first angiogram yields a negative result a second on another occasion reveals an aneurysm which for some reason did not fill previously.

If angiography shows an aneurysm or an angioma it is necessary to decide whether the lesion is operable, whether the patient's condition necessitates immediate operation or justifies delay, and what operation should be performed. These may be difficult questions calling for experience and good judgment.

The medical treatment of subarachnoid hæmorrhage consists of the relief of symptoms. It is doubtful if repeated lumbar puncture is of therapeutic value. If the patient is unconscious fluid must be given by drip or an œsophageal catheter used. Rest in bed will be required for at least three weeks.

Temporal Arteritis

The term temporal arteritis is applied to an obscure inflammatory disease of the blood vessels, particularly the arteries. It is not altogether appropriate, however, since the affection is not limited to the temporal arteries, but is usually widespread, and in some cases the temporal arteries may not be affected. Even the

term "cranial arteritis" is insufficiently descriptive. No term other than temporal arteritis, however, has so far been generally accepted. Recent contributions to the literature of the subject have been those of Cooke *et al.* (1946) and Cloake (1951).

Ætiology and Pathology. Beyond the fact that the disease occurs apparently exclusively in the elderly and aged, no causal factor is known. The inflammation appears to start in the adventitia and subsequently spreads to the media in which a giant-cell reaction may be excited. The media is also infiltrated by lymphocytes, plasma cells and large mononuclear cells. The intima shows marked thickening, but rarely any signs of inflammation and in the smaller arteries these changes are usually followed by a thrombosis which is rapidly organized and may be recanalized. Aneurysm formation does not occur. The characteristic lesions have been found in many arteries—the temporal and occipital and the retinal arteries and the aorta and its main branches and the coronary arteries and radial.

Symptomatology. A prodromal phase often occurs preceding symptoms relating to the arteries themselves. This is characterized by malaise, lassitude, weakness and pains in the muscles and joints. Fever is present which tends to become more pronounced when the vessels become involved. At this stage there is headache, which is severe, and corresponds to the distribution of the affected vessel. The scalp is tender and the patient appears to be in a state of great misery.

The inflamed arteries are palpably thickened, nodular and tender and these changes are particularly obvious in the superficial temporal arteries. There may be periarterial swelling and redness of the skin and the pulsation of the vessels is usually lost. This phase lasts for a week or ten days when the symptoms in and around the vessel begin to subside, but the artery may remain tender for a time.

The most serious of the common manifestations of the disease is involvement of the retinal arteries leading to visual loss which may be limited to a sector of the visual fields or amount to complete blindness in one or even in both eyes. The affected optic disc may be swollen and exhibit exudate, and even hæmorrhages. A retinal artery may be obstructed and œdema may extend to the retina beyond the disc. Later the appearances are those of secondary optic atrophy associated with retinal ischæmia. Ptosis and diplopia may also occur.

It is rather surprising that a disease which causes widespread

arterial thickening should apparently have so little effect on the brain, yet cerebral lesions are uncommon and usually only minor in character. Confusion, disorientation, impairment of memory, drowsiness and even coma may occur. Visceral arterial changes do not seem to lead to conspicuous symptoms, or it may be difficult to distinguish them from those of atheroma which are common in patients of the age at which temporal arteritis occurs. Venous thrombosis has been described.

The c.s.f. is usually normal, but may show a rise of protein. Hypochromic anæmia is common and erythrocyte sedimentation rate is usually raised.

Prognosis and Treatment. Most patients seem to make a good recovery, though this may take many weeks, and when the retinal vessels are attacked the resulting loss of vision is often permanent. Large doses of iodide have been said to be beneficial. Anticoagulants seem to be of no value. ACTH and cortisone often give symptomatic relief and their administration sometimes seems to mark the turning point of the disease, but they must be given with the caution usual in elderly patients. Excision of a section of the affected artery usually gives immediate relief.

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CHAPTER 11

MISCELLANEOUS CLINICAL AND THERAPEUTIC ADVANCES

Inclusion Body Encephalitis

THIS form of encephalitis has been recognized only during recent years, but already it is being reported with increasing frequency (Brain, Greenfield and Russell (1948), Greenfield (1950), Foley and Williams (1953)).

Pathology. The pathological features consist of perivascular infiltration and microglial hyperplasia with astrocytic gliosis in the cerebral cortex, basal ganglia and brain-stem. The characteristic lesion is widespread degeneration of ganglion cells, many of which show acidophilic hyaline inclusion-bodies in the nucleus and cytoplasm.

Ætiology. Inclusion body encephalitis is encountered during the first two decades of life, but most cases have been observed during the first decade. The occurrence of acidophilic inclusion-bodies suggests that it is probably due to a neurotropic virus which perhaps has affinities with the virus of herpes febrilis, but that is not itself the causal organism.

Symptomatology. In typical cases the disease runs a slowly progressive course lasting for from two to six months, in which three stages may be recognized. The first is characterized by predominance of psychological disturbances, such as change of mood, emotional instability and some intellectual deterioration which may be accompanied by attacks of petit mal or, occasionally, by generalized convulsions. In the second stage the patient lies in a state of stupor or akinetic mutism and exhibits symptoms of extrapyramidal disturbance, particularly complex involuntary movements which exhibit a striking periodicity. Such movements may be myoclonic, choreiform or ballismic. The third stage is one of decortication characterized by blindness and quadriplegia and in this stage the involuntary movements tend to grow less and may cease.

Pyrexia is often absent, or if present slight, during the early stages, but fever may occur towards the end. There is usually

a polymorphonuclear leucocytosis in the blood, and the cerebrospinal fluid usually has a normal cell and protein content, but a paretic colloidal gold curve is rather characteristic.

Characteristic changes have been described in the electroencephalogram. In the early stages the alpha rhythm is disturbed by four to six per second waves and occasional high voltage three per second waves are seen in the frontal region. Later high voltage slow waves are observed with periodic complexes synchronizing with the myoclonic jerks.

Thus, as stated above, the disease usually terminates fatally in from two to six months after the onset. Evidence is accumulating that chronic cases may occur, and since our pathological knowledge of the disorder has hitherto been gained exclusively from fatal cases it is possible that mild cases, in which recovery has occurred, have escaped detection. A cortical biopsy may be of value in establishing the diagnosis in doubtful cases.

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Subacute Sclerosing Leuco-Encephalitis

Van Bogaert (1945) has given the name subacute sclerosing leuco-encephalitis to a disorder which pathologically in certain respects resembles inclusion body encephalitis. Van Bogaert laid emphasis upon the occurrence of ill-defined areas of partial demyelination in the white matter accompanied by an infiltration with microglia, plasma cells and a diffuse gliosis. Greenfield (1950) states that demyelination may be present in inclusion encephalitis and inclusion-bodies have been found in Van Bogaert's disease. The clinical features of the two conditions appear to be identical and both Greenfield and Van Bogaert now accept their pathological identity. Van Bogaert has proposed, as a comprehensive name, "subacute sclerosing leuco-encephalitis" while Greenfield suggests "subacute sclerosing panencephalitis".

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Carcinomatous Neuropathy and Myopathy

One of the most striking recent additions to neurological knowledge has been the recognition of abnormalities in various parts of the nervous system and in the muscles, occurring in association with neoplasms of the viscera, but unrelated to metastases. These neuropathies and myopathies present many points of interest which are not merely theoretical, for the early recognition of these disorders may draw attention to the presence of a hitherto undetected neoplasm at a stage when it may still be amenable to treatment.

Denny-Brown (1948) under the heading "Primary Sensory Neuropathy with Muscular Changes Associated with Carcinoma" described two cases of a bronchial carcinoma in patients whose predominant neurological symptoms were gross loss of sensibility and an associated ataxia. Pathologically there were simple degeneration of the dorsal root ganglion cells and a primary degeneration of the muscles described as "polymyositis". Denny-Brown attributed these changes to the presence of a metabolic disorder related to the tumour cells and drew attention to their resemblance to changes associated with pantothenic acid and vitamin E deficiency in animals. Lennox and Prichard (1950) reported five cases of peripheral neuritis among 299 cases of carcinoma of the bronchus admitted to Hammersmith Hospital during the previous eight years. Autopsy in one case showed that the nerve lesion was a true peripheral neuritis with demyelination, predominantly motor, and not involving the brain or spinal cord. Brain, Daniel and Greenfield (1951) reported four cases of subacute cortical cerebellar degeneration in three of which there was also degeneration of the long tracts of the spinal cord. In these three cases there was also carcinoma which involved the bronchi in two and the ovary in one. A review of the literature showed a high correlation of carcinoma with subacute cortical cerebellar degeneration. Recent additions to the literature have been those of Henson, Russell and Wilkinson (1954) who reported 19 cases of carcinomatous neuropathy and myopathy associated with carcinoma of the lung in 17 cases and the breast and ovary in one each, and Heathfield and Williams (1954) reported a further four cases, all associated with carcinoma of the bronchus. The findings of these authors will be further described below.

Carcinomatous Neuropathy

Pathology. Subacute cerebellar degeneration associated with carcinoma is characterized pathologically by a mixture of changes in which degeneration of the dentate nuclei of the cerebellum is prominent. There may also be degeneration of the inferior olives, the subthalamic nuclei, the pyramidal tracts and the posterior columns of the spinal cord. In other cases of carcinomatous neuropathy other parts of the nervous system may be affected. Thus, in one of Henson, Russell and Wilkinson's cases the salient changes were degeneration and loss of motor neurones in the spinal cord and medulla. The picture was said to be that of a chronic progressive poliomyelitis. In cases with the clinical features of sensory neuropathy the characteristic pathological lesion is degeneration and loss of ganglion cells in the posterior root ganglia accompanied by degeneration of the peripheral nerves and the posterior columns of the spinal cord. Cellular infiltration of the meninges and perivascular cuffing of the vessels of the spinal cord have been observed. Nothing is at present known as to the nature of the association between these pathological changes and the presence of visceral carcinoma.

Symptoms. The time relation between the onset of the nervous symptoms and those of the carcinoma itself is important and in some cases puzzling. Sometimes symptoms of the carcinoma appear first and the signs of the neuropathy may be found on routine clinical examination or may develop later. Frequently, however, it is the symptoms of the neuropathy which bring the patient under observation, and further investigations then reveal the carcinoma. This seems to occur commonly in cases of subacute cerebellar degeneration associated with carcinoma of the ovary. At least one case has been observed in which the patient developed the neuropathy and made a good recovery from it before presenting symptoms of the carcinoma. At the other extreme comes a patient who did not develop subacute cerebellar degeneration until many months after an operation for removal of carcinoma of the ovary.

The clinical picture of subacute cerebellar degeneration is a striking one. Within a few months of the onset the patient may be bedridden and helpless from gross loss of function of the cerebellum with severe dysarthria and gross ataxia of both upper and lower limbs. Progressive dementia may occur after the onset of the cerebellar symptoms. Diplopia of the cerebellar type may be present and cramp-like pains in the legs have been noted. Symptoms and signs of cerebellar deficiency may be associated

with those of pyramidal degeneration resulting in a clinical picture closely resembling that of advanced disseminated sclerosis, but developing in some cases in a few weeks. The clinical picture of sensory neuropathy is characterized by numbness and sometimes pains and paræsthesiæ in the limbs with sensory loss of the polyneuritic type often with impairment of appreciation of posture, with diminution or loss of the tendon reflexes and sometimes muscular wasting. On the other hand the clinical picture corresponding to the pathological changes described above as chronic progressive poliomyelitis is wasting, weakness and fasciculation with diminution or loss of tendon reflexes which may be unaccompanied by sensory loss. A polyneuritic picture of any severity may accompany signs of cerebellar or pyramidal damage.

In general the disability is permanent and surgical removal of the carcinoma does not seem to bring about any improvement in the signs of involvement of the central nervous system, though the peripheral nerve changes may regress either spontaneously or after removal of the growth and have been observed to become worse again when the patient developed a recurrence.

Treatment. Beyond the fact that benefit as just noted may in some cases follow removal of the growth, no treatment is known to have any effect.

Carcinomatous Myopathy

Disorder of function of the muscles themselves may occur in the presence of visceral carcinoma either with, or without, the changes in the central nervous system described above.

Pathology. In Denny-Brown's cases the muscular changes were associated with sensory neuropathy. He described proliferation of sarcolemmal nuclei and increased cellularity of the connective tissue of a kind seen in chronic myositis or rapidly progressive myopathy. Heathfield and Williams describe changes similar to those observed by Denny-Brown in one of their cases, but in another case the only obvious change was an increase in the number of nuclei. Adams, Denny-Brown and Pearson (1953) speak of polymyositis associated with bronchial carcinoma, but Henson, Russell and Wilkinson in their series of cases found only changes which proved to be non-specific and often disproportionately slight in relation to the physical disability.

Symptoms. Patients with carcinomatous myopathy present with weakness and fatigability of the limbs and are found to have an atrophic paresis most marked in the limb girdles and proximal

parts of the limbs. No fasciculation is usually observed. Sometimes ptosis, diplopia and even bulbar paralysis occur. There may be a striking resemblance to myasthenia in those patients without pronounced muscular wasting and they may even show some degree of positive response to neostigmine. Adams, Denny-Brown and Pearson mention the association of skin changes producing the clinical picture of a dermatomyositis. The severity of the muscular weakness may fluctuate.

Treatment. Most treatments which have been tried seem to be ineffective, but Adams, Denny-Brown and Pearson speak of benefit being derived from ACTH and cortisone.

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Compression of the Median Nerve in the Carpal Tunnel

Since attention was drawn to this syndrome by Brain, Wright and Wilkinson (1947) it has come to be recognized as a common cause of disability, particularly in middle-aged women.

Ætiology. The median nerve is compressed where it runs through the carpal tunnel beneath the transverse carpal ligament in company with the flexor tendons. Three groups of cases can be recognized.

(1) *Spontaneous.* Most patients falling into this group are middle-aged women and the causal factors appear to be a combination of age and manual work, though precisely how the latter operates is at present obscure. The lesion is often bilateral and commonly one hand is affected before the other, usually the right in right-handed persons.

(2) *Associated with Bony Changes about the Wrist Joint.* In these cases a lesion of neighbouring bones, usually a fracture, often complicated by osteoarthritis, leads, in many cases only after a long interval, to compression of the median nerve probably by

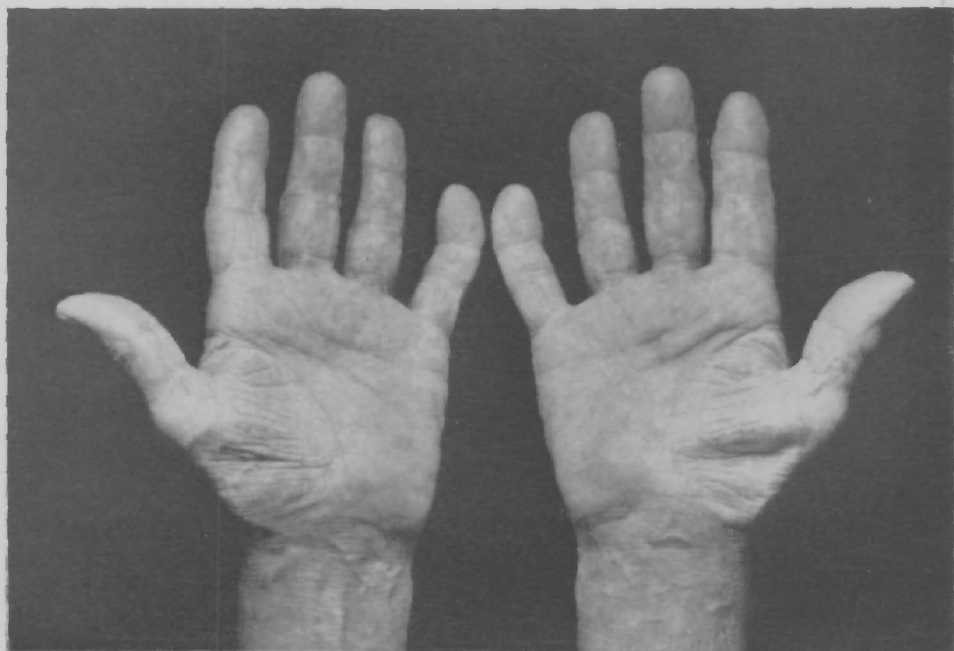


FIG. 18. Wasting of outer part of thenar eminences in compression of both median nerves.

narrowing the carpal tunnel. Such a lesion is usually unilateral and is seen more often in men than in women.

(3) *Acromegaly*. The tissue changes associated with acromegaly occasionally lead to compression of the median nerve in the carpal tunnel.

However the compression is produced the reaction of the nerve is the same, namely, swelling which usually extends for two or three cms. above the upper limit of the transverse carpal ligament. Indeed, the proximal part of the nerve is often more swollen than the part which lies in the carpal tunnel and which shows an indentation corresponding to the ligament. If the pressure is not relieved the end-result is a fibrosis with degeneration of the nerve fibres.

Symptoms. The initial symptoms are usually sensory, consisting of a burning and tingling sensation referred to the digits which receive their nerve supply from the median nerve, namely, the thumb, index and middle fingers and radial half of the ring finger. These uncomfortable sensations are often particularly prominent at night and tend to awaken the patient. They are soon followed by blunting of cutaneous sensibility which interferes with the manipulation of fine objects, e.g. a needle. At the same time weakness of movements of the thumb is usually noted, particularly opposition, and this adds to the handicap caused by the sensory loss. The patient may also observe wasting of the outer half of the thenar eminence. Occasionally pain is experienced on the volar aspect of the wrist and may be referred up the forearm.

On examination at this stage the hollowing of the outer half of the thenar eminence caused by wasting of the abductor brevis and the opponens pollicis muscles is conspicuous (Fig. 18) and their weakness is evident. Appreciation of light touch and pin prick and tactile discrimination are impaired over the cutaneous distribution of the median nerve, but not as a rule on the palm, since the palmar cutaneous branch usually leaves the trunk above, and lies anterior to, the transverse carpal ligament. Sometimes one of the affected digits is the site of an ulcer, or the scar of one, produced by a burn which was not felt at the time. Appreciation of passive movement is unimpaired. Occasionally pain is evoked by pressure on the volar aspect of the wrist.

Diagnosis. Difficulty in diagnosis is most likely to arise from confusion with other lesions causing acroparæsthesiæ. The commonest of these are cervical spondylosis and costoclavicular

syndromes. Cervical spondylosis often causes pain and paræsthesiæ referred to the digits. In such cases, however, the pain is usually felt in other parts of the upper limb from the shoulder downwards, sensory loss if present is not coterminous with the distribution of the median nerve nor is muscular wasting limited to the outer half of the thenar eminence. It is often absent in the hand in cervical spondylosis unless there is gross damage to the spinal cord at the cervical level associated with signs of involvement of the motor and sensory tracts. Some diminution in the tendon jerks in the upper limbs, especially the triceps jerk, is often found in cervical spondylosis and never in compression of the median nerve. The elucidation of the symptomatology of cervical spondylosis and compression of the median nerve in the carpal tunnel has greatly diminished the sphere of symptoms justly attributable to costoclavicular syndromes. If costoclavicular compression of the brachial plexus causes sensory symptoms only, these are not limited to the distribution of the median nerve. If, on the other hand, localized pressure on the inner cord gives rise to muscular wasting which involves the muscles of the thenar eminence, the accompanying sensory loss, or dysæsthesiæ, again is not within the median nerve distribution, but corresponds to that of the 8th cervical and 1st dorsal dermatomes. These clinical points are important in diagnosis. The X-ray changes of cervical spondylosis may afford useful confirmation, but it must be remembered that they are often present without causing symptoms in a patient of an age at which compression of the median nerve in the carpal tunnel commonly occurs. The muscular wasting does not often give rise to diagnostic difficulty. In pressure paralysis of the ulnar nerve the disability is often predominantly motor, but then the wasting in the hand is complementary to that associated with median nerve paralysis, namely, it affects the hypothenar muscles, the interossei and the adductor of the thumb sparing the abductor and opponens. Motor neurone disease is not accompanied by sensory symptoms and signs and in syringomyelia the sensory loss is of the dissociated type, sparing appreciation of light-touch, is not limited to the digits supplied by the median nerve, and is usually accompanied by more extensive wasting and diminution or loss of the tendon reflexes in the upper limbs.

Treatment. The only effective treatment of compression of the median nerve in the carpal tunnel is its decompression by surgical division of the transverse carpal ligament. This usually gives relief from dysæsthesiæ in a few days and if the condition

is not of too long standing complete sensory recovery may be expected in a few months. Good motor recovery also occurs except when muscular wasting and weakness have been present for several years.

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Liver Function and the Nervous System

During recent years considerable progress has been made in our understanding of the relationship between disordered liver function and disturbances of the nervous system in two main fields, namely, the mode of production of nervous symptoms by liver damage and the pathogenesis of hepatolenticular degeneration.

Neurological Complications of Liver Disease. Walshe (1951) described the neurological signs observed in 18 cases of hepatic coma. These included personality changes, mania and coma, with dilated pupils, choreiform movements of the arms, tonic grasping, and sometimes lead-pipe or cogwheel rigidity; absent abdominal reflexes, increased knee jerks, ankle clonus, and extensor plantar responses. In some cases there was either spasticity or lead-pipe rigidity of the legs. During the early phase of coma the patient sometimes adopted a characteristic posture, with the legs tightly drawn up to the abdominal wall. Walshe discussed various theories which had been put forward to explain these symptoms. He believed that hypoglycaemia might precipitate convulsions, but was not otherwise directly associated with the nervous disturbances. He discarded the theory that an intestinal toxin might pass through a damaged liver to enter the general circulation and also the theory that acetylcholine accumulates in the blood as a result of a fall in the plasma cholinesterase. He favours the view that the disturbed pattern of blood amino-acids which occur as the result of both acute and chronic liver failure may be toxic to the brain and suggests that in some cases interference may occur in the utilization of glutamic acid, with a consequent breakdown in the ammonia-binding mechanism of the brain. In a later paper Walshe (1958) further discusses disturbances of aminoacid metabolism following liver injury. His investigations led to a rather sharp division of the cases of acute hepatitis into two groups. The classical picture of the illness

occurring in a young adult with resolution of symptoms in a few weeks was commonly associated with a mild or moderate generalized aminoaciduria which cleared completely with the recovery of the patient. A second type of case, found more commonly among later age groups, was more insidious in onset and more prolonged and was associated with deep jaundice and negative, or very weakly positive, serum flocculation tests. These patients showed little or no disturbance of aminoacid metabolism.

The subject of hepatic coma is also reviewed by Adams and Foley (1953). They also describe the clinical picture in terms very similar to those of Walshe, but mention particularly "a peculiar intermittency of sustained muscle contraction that presents as an irregular flapping movement when the arms and legs are held out stretched. They describe the pathological changes in the nervous system, the most important of which is a diffuse hyperplasia of protoplasmic astrocytes in the cerebral cortex, lenticular nuclei, thalamus, substantia nigra, red, dentate and pontine nuclei, usually with little or no visible alteration in parenchymal structures. They favour the view that the underlying biochemical disorder is probably a disturbance of the metabolic cycle of glutamic acid.

Sherlock, Summerskill, White and Phear (1954), describing the neurological complications of liver disease as "portal-systemic encephalopathy", bring forward evidence that toxic nitrogenous substances passing from the portal vein into the systemic circulation—through a damaged liver, portal collateral channels, or both—can cause a diffuse cerebral disturbance sometimes culminating in hepatic coma. These authors also give a comprehensive account of the clinical picture, laying stress upon the psychological manifestations of the mild degrees of disturbance and the characteristic "flapping" tremor which was observed in 17 of their 18 patients. They classify their patients according to whether the neurological changes were persistent, transient, or terminal.

Investigations of liver-function, the portal-systemic venous collateral circulation and the blood ammonium level led to the conclusion that the important predisposing clinical factors were the portal-systemic venous collaterals, the hepato-cellular disease and nitrogenous substances in the intestines. They found elevated fasting blood ammonium levels in their patients and were able to reproduce the neurological disturbance by the use of a high protein diet and ammonium chloride. Identical changes followed methionine, and the elevation of peripheral blood ammonium could

always be correlated with the neurological state. The sensitivity of their patients to nitrogenous substances could be directly related to the presence of an abnormal route through which portal venous blood entered the systemic circulation without being metabolized by the liver. The pathway lay through a damaged liver, through portal-systemic collateral channels, or through both. They put forward the view that a nitrogen-containing substance in portal blood can thus cause a diffuse cerebral intoxication which they term portal-systemic encephalopathy.

They recommend that if a specific exciting agent can be identified it should be withdrawn or treated. Caloric requirements should be supplied with glucose delivered by the simplest route, and nitrogen intake, whether in food or drugs, should be reduced to a minimum. Chemotherapy may be used to reduce bacterial action in the intestines, and the bowels should be emptied with an enema, a daily action being ensured subsequently by an effective purge. They observed no benefit as a result of administering glutamic acid or sodium glutamate. They point out that high protein diet, casein hydrolysates, aminoacid supplements, and ammonium chloride are widely used in liver disease. These measures are not contraindicated, but their potential dangers must be recognized and anticipated.

Hepatolenticular Degeneration. During recent years a number of new facts about the metabolic disorders present in hepatolenticular degeneration have been discovered, but their essential nature is obscure. They concern (1) the excretion of aminoacid in the urine, (2) an abnormality of copper metabolism and (3) the therapeutic effects of the administration of BAL.

Excretion of Aminoacids in the Urine. The increased excretion of aminoacids in the urine in hepatolenticular degeneration was first reported by Uzman and Denny-Brown (1948) and the subject has recently been reviewed by Matthews, Milne and Bell (1952) and by Denny-Brown (1953). It has been shown by a number of workers that there is an increased urinary excretion of the ten essential aminoacids, although the serum aminonitrogen is not increased. It has also been shown that there is a diminished renal tubular reabsorption of the non-essential aminoacids, glycine and alanine. The aminoaciduria appeared to be present in all cases of hepatolenticular degeneration and has been found also in asymptomatic siblings of patients suffering from the disease. This strongly suggests that it is an inborn error of metabolism, but the nature of the defect has not been identified.

Abnormalities of Copper Metabolism. The pigmentation of the cornea, skin and other organs found in many cases of hepatolenticular degeneration first suggested the possibility that there might be an abnormal metabolism of heavy metals. Subsequently an abnormal concentration of copper was found in the liver and in the brain. Matthews, Milne and Bell state that, although there is evidence of some increase in the retention of copper in the liver in uncomplicated cirrhosis, the accumulation in hepatolenticular degeneration is greater in amount. They conclude also that there is considerable evidence that an abnormality of serum copper in cases of Wilson's disease is non-specific and inconstant. On the other hand increase of excretion of copper in the urine described by Mandelbrote, Stanier, Thompson and Thruston (1948) and Cumings (1951) does not appear to have been observed in other conditions. In this connection a distinction must be made between an increased urinary excretion of copper in proteinous and non-proteinous urine. Since it is believed that most, if not all, serum copper is contained in a single pure protein an increase in urinary copper in association with proteinuria could be explained by an abnormal leak through the glomeruli of the copper-protein normally present in the plasma. This, however, will not explain the greatly increased excretion in hepatolenticular degeneration where there is no proteinuria. Matthews, Milne and Bell put forward two possible explanations of this: owing to the increased amount of tissue copper in hepatolenticular degeneration hyperaminoaciduria may be effective in increasing the diffusible copper in the plasma, or there may be in hepatolenticular degeneration a defect of renal tubular reabsorption of the copper chelation complex in the glomerular filtrate in addition to the defective reabsorption of free aminoacid.

The Therapeutic Effects of BAL. Different experiences as to the therapeutic value of BAL in hepatolenticular degeneration have been reported. Denny-Brown (1950) (1953) and Cumings (1951) have observed definite improvement. Denny-Brown (1953) gives details of the dosage which he has found beneficial.

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The Treatment of Meningitis

The Choice of Chemotherapy

The appropriate treatment of meningitis depends upon the isolation of the causative organism and tests of its sensitivity to the various available chemotherapeutic agents. The chemotherapy of meningitis is a field in which, owing to the rapidity with which advances are being made, techniques are constantly changing. This is particularly evident at the moment in the chemotherapy of tuberculous meningitis. At any time a new development may render older methods out-of-date. All that can be done in a textbook, therefore, is to provide an up-to-date summary of the methods which, at the time of writing, are generally regarded as the best. First, a brief account of the dosage and method of administration of the principal chemotherapeutic agents now in use will be given. Unless otherwise stated the doses are those appropriate to adults and they must be reduced for children proportionately to their weight.

Antibiotics used in the Treatment of Meningitis

Penicillin. The intrathecal dose of penicillin is 20,000 units which may be given twelve-hourly if necessary. A systemic dose of 250,000 units six-hourly is usually sufficient.

Streptomycin. The usual intrathecal dose is 50 to 60 mgms. daily which is combined with 0.5 gm. intramuscularly.

Chloramphenicol. This drug may be given orally in doses described below for the treatment of influenzal meningitis. It can also be given intrathecally in a concentration of 100 micrograms/ml. up to a maximum of 750 micrograms daily.

Neomycin. The dose of this drug is 5,000 units intrathecally and 120,000 units intramuscularly.

Aureomycin. In addition to oral administration in the usual doses aureomycin can be given intravenously in doses of 7 to 10 mgms. per kilo every twelve hours.

Polymyxin. This drug is occasionally useful in the treatment of an infection with an organism which is insensitive to other antibiotics, e.g. pseudomonas. The dose is 5,000 units per pound intramuscularly four-hourly and the intrathecal dose is 20,000–40,000 units twice daily.

Intrathecal Administration of Antibiotics

In order to be effective an antibiotic administered intrathecally should have free access to the whole subarachnoid space and to the cerebral ventricles, into which it has been proved to penetrate after lumbar injection. Obstruction at any site may lead to a focus of infection which cannot be reached. Spinal block should be suspected when on lumbar puncture only small quantities of fluid can be obtained and it cannot readily be aspirated. This is an earlier sign of impending block than an abnormal Queckenstedt test and indicates the need for intraventricular injection. The aqueduct of Sylvius may become blocked or a cerebral abscess may develop—conditions which call for surgery. In all intrathecal medication the risk of introducing secondary infection should be borne in mind. Every precaution should therefore be taken to preserve asepsis. It is helpful to tabulate the results of the cerebrospinal fluid tests, its content of antibiotic, and the dosage and route of administration of the therapeutic agents used.

The Treatment of the Commoner Forms of Meningitis

Meningococcal Meningitis. The meningococcus is sensitive to the sulphonamides and to penicillin, but the response to treatment with sulphonamides is so good that penicillin is hardly ever needed. Sulphadiazine is the drug of choice. Treatment should begin with a loading dose of 6 grams for an adult, 3·5 grams for an adolescent and 2 grams for an infant. One gram is given four-hourly as a maintenance dose to an adult with proportionate reductions according to the age of the patient. If necessary part of the loading dose can be given intravenously. During the administration ample fluids—2 litres daily for an adult—should be given to prevent urinary blockage, and it is also helpful to keep the urine alkaline. The cerebrospinal fluid should be examined at frequent intervals so that progress may be noted or relapse detected. If there is no response to sulphadiazine in twenty-four hours the patient should be given one mega unit of penicillin two-hourly.

Pneumococcal Meningitis. Two alternative methods of treatment are available. The older method is to give 20,000 units of penicillin intrathecally every twelve hours at first, combined with 250,000 units systemically every six hours. Alternatively one mega unit of penicillin can be given two-hourly systemically. Treatment should be continued for a week.

Influenzal Meningitis. Chloramphenicol is the most effective drug. This drug when given orally has been shown to pass readily into the cerebrospinal fluid where it reaches concentrations ranging from 30 to 50 per cent of that in the blood stream. An initial loading dose of 25 mgms. per pound can be given orally followed by 15 mgms. per pound eight-hourly for fourteen days. Alternatively, streptomycin can be given in combination with sulphadiazine, the dose of streptomycin being 10 mgms. per pound intramuscularly every twelve hours and 50 to 100 mgms intrathecally daily.

Tuberculous Meningitis. The introduction of iso-nicotinic acid hydrazide (isoniazid) has already changed the treatment of tuberculous meningitis and may ultimately change it still further. Before this drug was introduced it was generally considered that streptomycin by intrathecal and systemic routes was necessary, the only important difference of opinion being on the frequency and duration of the intrathecal administration. In the routine practice introduced at Oxford a daily intrathecal injection of streptomycin was required for from six to twelve weeks and systemic treatment for at least six months, and possibly for longer. Since isoniazid penetrates readily into the cerebrospinal fluid the intrathecal administration of streptomycin has come to be regarded as of less importance than formerly. Smellie (1954) has reported a small series of cases of tuberculous meningitis in children treated by oral isoniazid and intramuscular streptomycin, without intrathecal streptomycin.

In the present state of our knowledge a suitable routine would be as follows. Streptomycin should be given intramuscularly in a dose of 10 to 15 mgms. per pound, or 1 gm. for adults, daily or later every third day for six months. The same drug is given intrathecally in doses of up to 50 mgms. daily for two weeks and then every other day, or every third day, for two months. Isoniazid should be given in combination with the streptomycin in oral doses of 1·5 mgms. per pound up to a maximum of 200 mgms. daily for the same length of time. Ashby and Grant (1955) recommend the use of cortisone.

The great drawback of the daily intrathecal administration of streptomycin, apart from the discomfort for the patient, is its irritating effect upon the spinal meninges with the production of a high protein and a pleocytosis in the cerebrospinal fluid independently of the effect of the infecting organism, and a tendency as a result to the formation of adhesions. These disadvantages are minimized by the new method. If spinal block develops it will be necessary to give the injection intraventricularly through burr holes, and the development of hydrocephalus will call for surgical treatment. Treatment is much facilitated if full details of the dosage of the drug administered, and details of the cerebrospinal fluid findings, are systematically recorded.

Long convalescence is required, particularly for patients with miliary or recent primary tuberculosis. Cairns recommends that when the acute phase is passed the possibility of surgical measures to eliminate an existing focus in another part of the body should always be considered, since patients with such persistent lesions tend to do badly.

The main index of a good response to treatment is the disappearance of tubercle bacilli from the cerebrospinal fluid.

The Chemotherapy of Neurosyphilis

The introduction of penicillin revolutionized the treatment of neurosyphilis and has now largely superseded other therapeutic agents. In this section we shall deal first with the routine treatment of neurosyphilis with penicillin, then with the risks of a Herxheimer reaction and attempts to prevent it, thirdly with the desirability of supplementing penicillin with other therapeutic agents and, lastly, with the indications of the arrest of the disease or the need for further treatment.

Routine Treatment with Penicillin. The standardization of penicillin treatment has recently been discussed in a World Health Organization Technical Report (1952) and the conclusions drawn from ten years treatment of syphilis with penicillin has been reviewed also under the auspices of the World Health Organization (Idsoe *et al.*, 1954). The preparation which has been most widely used in recent years is a suspension of procaine penicillin in oil containing 2 per cent aluminium monostearate (P.A.M.) by the standard requirements which have been fixed by WHO. It has been the practice to employ larger doses of penicillin in the treatment of neurosyphilis than for most other conditions and when a watery solution of penicillin is used it is generally given in a dose

of 500,000 units intramuscularly twice a day for ten or twelve days. When P.A.M. is employed, though the total dose is only slightly less, 9,000,000 units, it can be given at longer intervals, 600,000 units being administered every second day. There is no need to give intrathecal injections of penicillin in the treatment of neurosyphilis.

The Risks of Herxheimer Reactions. Herxheimer reactions are fortunately rare in the treatment of neurosyphilis with penicillin. It is unlikely that they can be prevented by beginning the course of penicillin with a small dose. Some consider it wise, whenever possible, to give a preliminary course of bismuth for a few weeks before starting the penicillin. This may be particularly desirable in any case in which on clinical grounds it is thought that the Herxheimer reaction if it should occur would be particularly serious, but the risk, which is slight, must be weighed against the possible disadvantage of a few weeks delay in beginning a form of treatment as effective as penicillin. In any case it is stated that bismuth will not prevent a Herxheimer reaction in general paresis, which is consistent with its therapeutic ineffectiveness in that disease.

The need for Supplementary Treatment. There is a difference of opinion as to the adequacy of penicillin alone for the treatment of general paresis. Some workers, Dattner (1948), Curtis, Kruse and Norton (1950), Hahn (1951) believe that, with the possible exceptions mentioned below, penicillin alone yields therapeutic results as good as, or better than, malaria and at less risk to the patient, and that there is therefore no object in giving malarial therapy in combination with penicillin. Others believe that the results when penicillin and malaria are given in combination are better in general paresis than those achieved by either alone. A recent enquiry showed that this combined therapy is still widely used both in Europe and in America. It is possible that differences in the results obtained depend in part upon differences either in the severity of the disorder or in the stage at which treatment is begun, for example, that in many instances cases of general paresis treated in mental hospitals are more severe than those treated in neurological clinics, but there is no evidence on this point. In our view for the average case of general paresis penicillin alone is the treatment of election, but malaria may suitably be used when the response to an initial course of penicillin is disappointing.

Syphilitic optic atrophy is notoriously refractory to treatment

and here again some workers, Curtis, Kruse and Norton (1950), Hahn (1951), prefer to give penicillin and malaria in combination rather than penicillin alone, but Kenney and Curtis (1953) conclude from a follow-up of 37 cases of syphilitic optic atrophy, some treated with penicillin alone and some with penicillin and malaria, that the evidence does not justify the use of malaria for the treatment of early cases. Here if malaria is to be used at all it is rational to use it as early as possible since even a few weeks delay may mean a serious deterioration in vision.

The Supervision of the Treated Case. The most desirable result of treatment is clinical improvement, which in neurosyphilis is usually more obvious in the sphere of symptoms than of physical signs. Little change in the latter is to be expected even though the disease is arrested by treatment. In these circumstances changes in the cerebrospinal fluid and in the serological reactions of the blood play an important part in the estimation of the response to treatment, but it must be borne in mind that after a single course of penicillin improvement in the cerebrospinal fluid and in the serological reactions may continue for a long time. Ingraham, Stokes and Gammon (1950) found that changes in the fluid occur most quickly during the first year and level off in the third year. Alterations occur most rapidly in tabes and slowest in paresis and taboparesis. By the end of the fifth year the fluid was normal in 55 per cent of paretics and taboparetics and 60 to 70 per cent of tabetics. "Fluid relapses" occurred after the third or fourth year in 5 per cent. A convenient routine, therefore, is for the tests to be carried out before treatment is begun and if the patient's clinical condition is satisfactory they need not be repeated for six months. If at the end of that time they show improvement, a further period of six months is allowed to elapse and the tests are then carried out again. By this time there is in most cases a substantial improvement, which is a contraindication to a further course of treatment. The patient is then kept under clinical review and examinations of the cerebrospinal fluid and the serological tests are repeated at the end of a further year and then, if the patient's condition remains satisfactory, probably at the end of a further two years and again two years later. A diminution in the cell and protein content of the cerebrospinal fluid is the earliest, and most reliable, sign of improvement: next comes a return towards the normal of the colloidal gold curve in general paresis and, lastly, improvement in the serological reactions. In general, therefore, a second course of treatment will not be called for within

a year of the first unless there is obvious clinical deterioration or unless the various tests show no substantial change for the better.

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The Drug Treatment of Epilepsy

The recent introduction of new drugs for the treatment of epilepsy has added to our therapeutic weapons, but it has also made it important for those who use them to know the indications for their use, especially as some of them sometimes have toxic side-effects. The subject has recently been reviewed by McNaughton (1954) who has well set out the general principles governing the drug treatment of epilepsy.

General Principles. These are (1) that there are wide individual differences in the response to drugs and each patient must be treated on a trial-and-error basis. That is to say the physician must be prepared repeatedly to modify the treatment until the best results obtainable in any individual case are achieved. (2) The choice of drugs depends to some extent on the type of epilepsy and in this connection both the clinical features and the EEG. abnormality must be taken into account. (3) Drug dosage depends upon the frequency and severity of the attacks, the aim being to achieve complete control of the attacks with the lowest possible dosage and with as few undesirable side-effects as possible. It is necessary to recognize that unfortunately this cannot always be achieved, in which case it may be undesirable to increase the dosage of drugs beyond a certain point. (4) The simpler and safer drugs should be tried first, hence it is best to begin in most cases with phenobarbitone, given in a dose of $\frac{1}{2}$ grain two or three times a day. If this is ineffective it is necessary either to increase the dose of phenobarbitone or to add one of the other drugs or, in some cases, to do both. Different drugs, or combinations of drugs, may

need to be tried until it is certain that the best possible results have been achieved. (5) Drug therapy should be continuous and the patient should be warned not to give up the drugs without medical advice since such a withdrawal may precipitate status epilepticus. Any change in drug dosage should be made gradually. (6) It happens occasionally that the patient becomes increasingly tolerant of a particular drug or a combination of drugs, that is to say the dose gradually needs to be increased to produce its original effect, or the drug may lose its efficacy altogether. In such cases a change of medication is necessary. (7) The patient should be asked to keep a record of all attacks and it is useful to give him a form designed for this purpose.

The Barbiturates. The two barbiturates chiefly used in the treatment of epilepsy are phenobarbitone and methyl-phenobarbitone. Both are too well known to need detailed discussion here. Methyl-phenobarbitone is occasionally effective when phenobarbitone fails and is usually well tolerated, but occasionally after only a few doses the patient exhibits toxic symptoms, especially drowsiness and ataxia.

Phenytoin Sodium (also known as soluble phenytoin, diphenylhydantoin sodium, phenantoin, dilantin sodium, epanutin, eptoin) (Tabing, Gayle and Hawkins, 1947). This seems to be the most useful anti-convulsant drug after phenobarbitone and has the advantage that it produces little or no sedative effect. It is prescribed alone or in combination with phenobarbitone. The dose is gr. $\frac{3}{4}$ to gr. $1\frac{1}{2}$ and the maximum dose usually tolerated by an adult is gr. $1\frac{1}{2}$ three times a day, though occasionally a patient may be able to tolerate as much as gr. $7\frac{1}{2}$ daily. This drug is most effective in the control of major epilepsy, but it is sometimes helpful in cases of petit mal and psychomotor epilepsy.

The principal toxic effects are hyperplasia of the gums (Fig. 19) which is rarely troublesome except in patients taking large doses, hirsuties, and skin eruption of a morbilliform type which is said to occur in up to 5 per cent of patients. This usually subsides after withdrawal of the drug. In such cases the drug may be tried again cautiously, but if the rash recurs its use must be abandoned. Severe dermatitis is fortunately rare. Toxic effects on the nervous system are also uncommon, but confusion, drowsiness and ataxia are occasionally encountered, quickly disappearing after withdrawal of the drug. Gastric discomfort is usually attributed to the alkalinity of the drug and this symptom can sometimes be eliminated by giving the drug with a meal. Serious blood disorders are



FIG. 19. Hyperplasia of gums due to phenytoin.

extremely rare, but attention has recently been drawn to the possibility that there may be an association between the administration of sodium phenytoin and the development of a megalocytic anaemia (Hawkins and Meynell, 1954).

Methoin (also known as mesontoin and mesantoin). This drug, closely related chemically to phenytoin and given in similar doses, has sometimes been found more effective than phenytoin in controlling major attacks. It is also less likely to produce hyperplasia of the gums, but more likely to cause drowsiness. Like phenytoin it may cause a rash, and severe exfoliative dermatitis has been reported. It has produced agranulocytosis and aplastic anaemia (see below). (Kozol, 1947, Mallin and Gammon, 1953).

Troxidone (also known as trimethadione and tridione).

Paramethadione (paradione). These drugs were introduced as the result of experimental studies in animals, when they were tested against convulsant drugs. They are particularly effective in controlling attacks of petit mal. The average dose of both is 5 grains (0.3 gm.) and it is wise to begin gradually with one dose a day, increasing up to the limit of tolerance if smaller doses are ineffective, the maximum daily dose being 35 grains (2.1 gm.). These drugs should be given a thorough trial in patients with brief seizures of any type associated with 3 per second bilaterally synchronous wave-and-spike patterns in the EEG. The drugs are also sometimes effective in controlling myoclonic seizures. Either of these drugs may precipitate a major attack in which case it is advisable to add phenobarbitone. McNaughton states that the diones may be given in combination with phenytoin in patients who have both petit mal and grand mal, but the adjustment of these two drugs may prove difficult in practice since they often appear to be mutually antagonistic.

The two toxic effects of which patients most complain are gastrointestinal disturbances, especially nausea, and a sensation of glare in bright light which may be reduced by wearing dark glasses. Skin rashes have been reported and either drug may produce agranulocytosis or aplastic anaemia (see below). (Davis and Lennox, 1947, 1949).

Mysoline. Mysoline or primidone is another dione derivative which has recently been introduced, the dose being 0.25 gm. The average daily dose for adults is three to six tablets, Butter (1953) reports a trial of this drug, and he found that 50 per cent of 58 epileptics treated for grand mal for 15 months derived benefit. Most patients complained of drowsiness for a day or two and in

eight cases the persistence of this symptom necessitated the withdrawal of the drug. Apart from this toxic symptoms and signs were few and transitory. Petit mal attacks were reduced by half in 23 per cent of cases and one patient with psychomotor attacks showed great improvement. Gastrointestinal disturbances and a skin rash are occasionally observed. An over-dosage may cause drowsiness and ataxia. The makers, Imperial Chemical (Pharmaceuticals) Limited, state that no serious side-effects have been encountered and routine blood counts and urine examinations over extended periods have shown no abnormality.

The Effects of Anticonvulsant Drugs on the Blood. The most serious toxic effects of anticonvulsant drugs are upon the bone marrow leading to agranulocytosis or aplastic anæmia, as described above. It is generally recommended that patients taking methoin, troxidone or paramethadione should have regular blood examinations which should be carried out two weeks and four weeks after the administration of the drug has begun and thereafter at monthly intervals as long as it continues. It must be borne in mind, however, that the blood changes may occur very rapidly and therefore routine blood examinations at regular intervals are not likely to detect the fulminating case. They will, however, draw attention to more gradual depression of blood formation and therefore act as a warning. Patients taking these drugs, however, or a relative in the case of children, should be instructed to report to the doctor any sudden deterioration of health, particularly symptoms of an infection.

The Management of Status Epilepticus

Status epilepticus is a serious complication of epilepsy which may terminate fatally. The essential part of its treatment is the administration of suitable sedatives as early as possible. Phenobarbitone sodium given in a dose of 2 to 4 gr. intramuscularly or subcutaneously, followed by a dosage of 2 gr. every hour for several hours, may be sufficient, but paraldehyde is usually more effective if given in doses of 1 to 4 drams per rectum or 5 to 10 ml. intramuscularly according to weight. McNäughton states that some patients respond rapidly to intravenous sodium amytal $3\frac{3}{4}$ to $7\frac{1}{2}$ gr. and intravenous tridione 0.1 grm. in 5 ml. of water has also proved effective with major convulsions as well as with petit mal status. Lumbar puncture sometimes seems helpful and hypertonic glucose and sucrose can be given intravenously.

Patients with status epilepticus require careful nursing. They should be nursed flat and preferably in the semi-prone position, attention being paid to maintaining a clear airway. Hyperthermia must be avoided by promoting heat loss, and dehydration prevented by giving adequate fluids, if necessary by intravenous or subcutaneous drip or by stomach tube. Antibiotics may be required as a prophylactic against pneumonia.

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The Treatment of Myasthenia Gravis by Thymectomy

The subject of myasthenia gravis has recently been reviewed by Adams, Denny-Brown and Pearson (1953), pathological changes in the striped muscles have been described by Russell (1953) and the value of surgical treatment has been discussed by Keynes (1946, 1949, 1954), Viets (1950) and Eaton, Clagett and Dastron (1953). Keynes (1954) in his most recent paper stresses the importance of distinguishing patients suffering from myasthenia who have a thymoma from those who have not. He believes that the approach to the two types of the disorder should be different and that in the past confusion as to the results of thymectomy has arisen from a failure to separate them. In his experience the mortality rate of the operation is small. By July, 1949, Keynes (1949) reported the results of a follow-up on 120 patients who had undergone thymectomy. The results were:—

A. Well	39	32.5%	} 65.8%
B. Greatly improved	40	33.3%	
C. Somewhat improved	31	25.8%	
D. No better	10	8.3%	

He states that since 1949 with more than 200 patients without thymomas to be assessed the results have remained very much the same or, if anything, slightly better. An independent investigation of 100 of his patients, carried out in 1951 to 1952, showed 41 of 93 patients in category "A" with 26 in category "B", i.e. an excellent result in 67, or nearly 70 per cent. Eaton and Clagett (1950) in the light of their surgical experience at first maintained that thymectomy did not influence beneficially the course of myasthenia gravis. Later, however, Eaton, Clagett and Bastron (1953) published a table which showed that patients who had been operated on did better than those who had not. They found that "50 per cent of the thymectomized patients who survived operation had, more than three years and eight months later, experienced results justifying the risk of operation, while only 29.2 per cent of the control patients had obtained comparable results". They draw from these figures, however, the cautious conclusion that "it cannot be concluded that removal of the thymus itself influences beneficially the course of myasthenia gravis. It is possible that the operation itself stimulates certain endocrine metabolic processes within the patient and accounts for the favourable results". They conclude "that the basic disturbance in endocrine metabolism which probably gives rise to myasthenia gravis also gives rise to the changes in the thymus characteristic of myasthenia gravis and that these processes can be disturbed by removal of the thymus in such a way as in time to lessen the severity of the disease". Keynes describes this as "a wonderful example of the twisting of a plain fact into a complicated theory in order to suggest that the operation of thymectomy is not what it appeared to be". From the patient's point of view at any rate the fact is more important than the theory and there is no doubt that the work of Keynes and others in this field have established the value of thymectomy in the treatment of myasthenia.

Should operation be recommended in every case? Certainly in the majority of cases it should. An exception may perhaps be made in those cases in which the disease is already of long standing and limited in its distribution, for example, the ocular muscles, and there is no reason to suspect a thymoma. Such patients may remain unchanged for many years and if, as sometimes happens, the disease has already been present for many years when they come under observation it is probable that the changes in the ocular muscles are irreversible, or to a large extent so, and that therefore they will not benefit subjectively from operation.

It is a common experience for a patient who has been operated on to continue to need neostigmin, perhaps even in the pre-operation doses, for some time. Keynes points out that on the whole, as time passes, that patients tend to progress from category "C" to "B" and from "B" to "A". A few have relapsed from "C" to "D", very occasionally from "B" to "C", but never as yet from "A" to a lower category. The time factor in recovery is, therefore, he points out, very important. Sometimes recovery takes place very rapidly: at others it may start quickly and then slow down, the full result not becoming established for months or even years.

Keynes (1954) states that not more than 15 per cent of myasthenic patients are found to have thymic tumours, but his early experience with the bad results of surgery in these cases led him to substitute high voltage X-ray therapy for primary operation. Of 41 patients treated for thymomas, all the earliest ones treated surgically had died, but of the 26 treated first with deep X-rays 20 had had a subsequent removal of the tumour with the following results:

Quite well and symptomless	.	.	.	.	.	4
Considerably improved	.	.	.	.	.	8
Initial improvement and then relapse	.	.	.	.	.	3
No better	.	.	.	.	.	1
Died	.	.	.	.	.	4

The necessity for avoiding primary operation for tumours stresses the importance of carrying out careful X-ray examinations in order to detect the presence of a thymoma which can usually be done if a correct exposure is given in the correct position, the lateral ones being of much greater importance than the antero-posterior. Tomography may occasionally be of value.

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CHAPTER 12

ELECTROENCEPHALOGRAPHY

by

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History

ELECTRICAL activity in the brains of living animals was first observed in 1875 by Caton working at Manchester. For some time the spontaneous rhythmic activity which could be recorded from electrodes placed on the cortex was considered of little relevance and excited much less interest than the *evoked* potentials which signalled the arrival of impulses up afferent pathways. Gotch and Horsley in 1892, using the electrical method, began the series of investigations which later led to the mapping of function in the whole sensory cortex. At this time neurophysiology as a science began. The study of both *evoked* potentials and spontaneous rhythmic activity was at first handicapped by the inertia and insensitivity of the recording devices of that time. No amplification was available. The capillary electrometer and Einthoven's string galvanometer were sensitive instruments with little inertia. Using the latter, Neminski in 1925, described two spontaneous rhythms from the dog's cortex, which were the analogues of the "alpha" and "beta" rhythms of the human brain later discovered by Berger (1929). Berger began his work with a string galvanometer and later acquired a thermionic valve amplifier which enormously increased the size of his records. He showed that it was possible to record the electrical activity of the cortex through the intact skull and scalp. For these records he coined the term "elektro-enkephalogram"—in English, electroencephalogram, abbreviated to EEG. The term, electroencephalogram, (EEG.), has since been accepted throughout the world to describe records obtained from the scalp, in distinction to "electrocorticogram" (ECoG.), which describes records obtained from the exposed cortex.

Berger's observations were fully confirmed by Adrian and Matthews at Cambridge in 1934 (a). By this time the perfection of

valve amplification and the development of the cathode ray oscillograph (CRO) made possible the recording of potentials of any size or frequency, and enabled multi-channel apparatus to be built suitable for recording from many areas of the head at the same time. Permanent long records were necessary and since the photography of the CRO records was an expensive procedure, high performance ink-writing oscillographs came into general use as soon as the subject aroused clinical interest. Berger had already explored the clinical field very thoroughly, but his results suffered from the limitation imposed by the use of a single channel recorder, and since he placed his electrodes very widely apart—on frontal and occipital regions, he had been unable to locate the potentials he recorded. Using the location method devised by Adrian, with which he had shown that the main rhythm of the human EEG. has a location in the visual association areas, Walter first successfully located cerebral tumours at Maida Vale in 1936. Meanwhile, in America, Gibbs, Gibbs and Lennox (1937), began their extensive work on the EEG. characters in the epilepsies. With the advent of the war, the fundamental physiological work upon which understanding of the phenomena must depend, was largely halted, but the last eight years have seen a great increase in activity throughout the world with results that are already of absorbing interest. Nevertheless, although little fundamental neurophysiology was done during the war, a large accumulation of clinical data had been amassed and electroencephalography had been found to have wide clinical application. To extend his knowledge, the reader is referred to the larger works on this subject (Gibbs and Gibbs, 1950; Schwab, 1951; Hill and Parr, 1950).

The Nature of Spontaneous Activity

There can be no doubt, as Berger claimed, that the rhythmical activity recorded from the human scalp is produced by the neurones of the cerebral cortex, but compared with the brief electrical change observed during the passage of the impulse down a single axon these changes are immensely slow. As Adrian demonstrated in the case of isolated ganglia from the gold-fish, probably any aggregate of neurones can be induced to develop slow rhythmic discharges under certain conditions. Such conditions include uniform stimulation and a constant physico-chemical milieu. Any change of stimulus intensity may cause the rhythmical potentials to cease. It therefore seemed likely to Adrian and Matthews that the phenomena of the human cortex were of this nature—the spon-

taneous beat of an area of occipital cortex, the neurones being synchronized in some way. By applying a metal heated to 65°C., Murphy and Dusser de Barenne (1941) killed the outer layers of the cortex and showed that spontaneous activity was chiefly dependent upon the fifth and sixth layers, since only when these were destroyed was the ECoG. abolished. There are three possible theories to account for the EEG. (Bremer, 1949). The waves may be the manifestation of an autorhythmicity of the cortical cells and particularly those of the large pyramidal cells of the deeper layers. Secondly, they may result from a rhythmical stimulation of the cortex by volleys of impulses from a diencephalic pacemaker. A third hypothesis suggests that they reflect a periodic conduction through the cortex of trains of impulses travelling in *reverberating circuits* of neurones. The early work which indicated that undercutting the cortex or destruction of sensory projection nuclei of the thalamus abolished the EEG. in the area of cortex concerned, made the idea of reverberation in thalamo-cortico-thalamic circuits attractive. Following this conception, McCulloch (1947) has suggested that the alpha rhythm of the occipital cortex may have the function of a scanning mechanism transforming the multiple cortical responses to peripheral stimuli on to a single time ordinate rather after the manner of the television camera. There are, however, objections to this view. Bremer (1937) showed that while section of the thalamo-cortical fibres in the cat certainly reduces the size of spontaneous cortical activity, the latter are by no means abolished. The residual activity left after transection can be greatly increased by the local application to the cortex of 1 in 1000 strychnine. Kristiansen and Courtois (1949) have also shown that in the cat after removal of one thalamus, or after undercutting the cortex there is as Dusser de Barenne and McCulloch (1938) claimed, an immediate cessation of spontaneous activity at the cortex. But after an interval of some hours, the spontaneous activity reappears with reduced size. This experiment was repeated on pieces of cortex, not only undercut but isolated from the rest by a circular incision, with insulating material inserted between the isolated piece of cortex and the remainder. Provided the blood supply was preserved, rhythmical electrical activity could again be recorded after some hours from the isolated cortex. Nevertheless, there can be no doubt that thalamic activity, as well as the activity of the midbrain structures and the sensory systems can greatly modify the spontaneous activity of the cortex.

Influence of thalamic activity on the cortex. Spontaneous

rhythmic activity having characters very similar to that of the cortex has been recorded from the thalamus by many workers (Morison, Finley and Lothrop, 1943). As already indicated, thalamic destructive lesions and section of the thalamocortical fibres produce an immediate reduction of cortical activity. Similarly, cortical lesions influence, but to a much lesser extent, the spontaneous activity of the thalamus. But the interaction between cortical and thalamic activity is not a complete one. There is some degree of thalamic and cortical independence. In a symposium on thalamo-cortical relationships, Earl Walker, Rose and Woolsey, Jasper, Bishop and others, reviewed present knowledge (1949). Sometimes slow waves may be present in the thalamus at a time when fast waves can be recorded from the cortex. The burst activity which may have similar frequency in thalamus and cortex is not necessarily synchronized in time. This condition of "semi-independence" has been described by Morison and Dempsey (1943). Stimulation of thalamic areas may have profound effect upon the activity of the cortex. Morison and Dempsey (1943) first showed that stimulation of the thalamic reticular system resulted in remarkable control of the cortical electrical activity. This work has been followed by Jasper and his colleagues (1948, 1949). The area from which control over the cortex can be obtained is confined to the small area of the intralaminar region. A single electrical pulse of one or two msecs. duration and 3-5 volts intensity to this area of the cat's thalamus sets up a train of rhythmic waves in widespread areas of both sides of the cortex. The form and frequency of this induced rhythm is very similar to that of the spontaneous alpha rhythm of the human EEG. (Jasper, 1949a). The induced rhythm appears first in the frontal areas and after a second or so spreads to the occipital areas. Stimulation of different points within the intralaminar system results in the appearance of rhythmic activity in different areas of the cortex, on one or both sides. With repetitive stimulation at a frequency approximating to that of the spontaneous cortical rhythms a gradually increasing response (recruitment) is witnessed. Jasper and Fortuyn (1947) found that stimulation at 3 a second from a number of different areas of the intralaminar system produced widespread bilaterally synchronous slow waves or spike and waves—the pattern associated with petit mal in humans. This type of response was most readily obtained from points near to the anterior pole of the dorsomedial nucleus or in the nucleus centralis lateralis. The bilateral spike and wave cortical responses are occasionally

seen as an after-discharge following intense stimulation. Since cortical ablations have no effect upon the spread of the cortical responses it would appear that the spread is within the thalamus. Spread from one side of the brain to the other was not altered by section of the corpus callosum or of the anterior or posterior commissures, but was prevented by section of the massa intermedia in some experiments. The exact pathways of spread from one hemisphere to the other are not known. The long latencies for the spread from one cortical area to another—one second or more, suggested to Jasper (1949) that the spread must be through a multisynaptic system.

Relationships between evoked and spontaneous activity. The cortical projection areas for all the sensory modalities have been extensively studied. Only brief reference will be made here to the principles involved. The initial surface-positive wave which signals the arrival of impulses in cortical layers IV and V, is followed by a surface negative wave which signals the departure of afferent impulses. This is best seen in the lightly anaesthetized animal. In such an animal a rhythmic series of waves then follows in the cortex as an after-discharge. In deep anaesthesia the arrival of a series of surface-positive waves leaves the slow rhythmical spontaneous activity unaffected. In lighter anaesthesia each surface-positive wave may cause a slight change or "resetting" of the spontaneous activity. In waking animals or in man, stimulation of the retina by flickering light of high intensity repeated with a frequency approximating to the spontaneous activity of the occipital cortex (alpha rhythm), may cause a rhythmic response in the cortex at the stimulus frequency or at a harmonic of it. This is the classical "driving of the alpha rhythm" described by Adrian, who considered the phenomenon to be dependent upon the activity of the visual receptor area 17 since he was able to induce "following" better on one hemisphere by stimulating only the opposite half of the visual field (1947).

The relations between the evoked activity of the specific projection systems and the activity of the thalamic reticular system has been investigated by Jasper (1949) in three ways:—

(a) Simultaneous stimulation of the thalamic reticular system while recording evoked potentials in primary cortical projection areas.

(b) Simultaneous stimulation of the reticular system while recording cortical responses to local thalamic stimulation within sensory relay nuclei.

(c) Destruction of sensory relay nuclei followed by reticular stimulation.

The thalamic reticular system had no influence upon the *primary* cortical potentials evoked by stimulation of the sensory relay nuclei but the after-discharges following the primary potentials were completely suppressed when the reticular system was stimulated. Jasper states: "It seems clear that the reticular system is unable to block the arrival of afferent impulses to the cortex, but may affect their elaboration through transcortical and thalamo-cortical circuits." However, although stimulation or destruction of the thalamic relay nuclei did not influence the rhythmic activity of the cortex, stimulation of afferent pathways in medial or lateral lemnisci produced responses within the intralaminar thalamic areas, and caused some control of cortical activity. The connections between specific afferent pathways and the intralaminar reticular system must, therefore, be distal to the specific relay nuclei in the thalamus.

Influence of hypothalamic and midbrain activity. The EEG. of the unanæsthetized cat with complete transection of the upper midbrain which removes the whole sensory influx except the first and second cranial nerves has a pattern like that of the intact cat asleep or a normal cat under barbiturate anæsthesia (Bremer, 1935). The animal is, in fact, asleep and cannot be woken. Section lower down the brain stem to leave the cranial nerves intact, results in a similar EEG. pattern, and a sleeping cat, which can, however, be woken by sensory stimulation by, for example, sound stimuli. In the cat the pattern of such sleep states, natural or induced by anatomical section ("coup Bremer"), is one of rhythmical bursts of slow waves, occurring fairly regularly with spaced intervals of relative absence of activity. The pattern of wakeful alertness is one of generalized low voltage fast activity in the EEG. Lindsley, Bowden and Magoun (1949) studied the effects of lesions placed at different levels in the brain stem of cats whose brains had been "isolated" by section at the upper end of the cord. Elimination of the pons had little effect, some rhythmical bursts occurred after lesions at this level, but the most marked effect occurred after discrete lesions in the midbrain tegmentum or basal diencephalon. After the latter the cat's EEGs. resembled those of normal sleep or barbiturate anæsthesia. The burst activity recorded from the cortex could also be recorded from the intralaminar areas of the thalamus and the latter were abolished by acute decortication, again emphasizing the mutual semidependence of

cortical and thalamic activity. In another study Moruzzi and Magoun (1949) mapped the areas in the midbrain and basal diencephalon, stimulation of which abolishes the slow wave bursts of the sleep state and produces the low voltage fast activity of the "activated" EEG. These areas lie in the midbrain tegmentum, posterior hypothalamus and subthalamus, the whole comprising the "ascending reticular activating system". The responses induced by stimulation of this system are not mediated by any known ascending pathways that traverse the brainstem, but may be mediated by the intralaminar reticular system of the thalamus, already discussed, for rhythmical activity within this system is also prevented by stimulation in the midbrain.

Earlier Murphy and Gellhorn (1945) had shown an arousal effect upon the cat's cortex from stimulation of those hypothalamic points from which peripheral sympathetic effects could be obtained. This effect consisted of an increase in fast rhythm which persisted long after hypothalamic stimulation ceased. The cortical effects were mediated by intracerebral pathways since section of the medulla had no effect upon them. The pathway from hypothalamus to cortex was found by Murphy and Gellhorn to be through the dorsomedial nucleus of the thalamus. This may be a part of the same system, associated with emotional activity, by which arousal of the cortex is brought about. It is obvious, as all these workers point out, that these studies throw a great deal of light on the problems of normal sleep, and the cortical arousal to stimuli in the waking state.

Development of Cortical Patterns

At birth little rhythmical activity is apparent in the EEG, unless the child is asleep. Development of the patterns at the start of life has been studied by Smith (1938), and for the later years of childhood by Lindsley (1939) and by Henry (1944), the latter's work being the only extensive systematic work on this subject. There are, however, large gaps in knowledge. By the sixth month of life rhythmic activity is apparent both from the sensorimotor cortex and from the occipital cortex, the two rhythms having slightly different frequencies. The rhythm of the occipital cortex, later to be the 8-13 c./sec. alpha rhythm, increases in frequency at first rapidly, the changes following an exponential curve (Lindsley, 1939). The period from the first to the tenth year is one of great complexity in the EEG., each area showing a complex mixture of waves of different frequencies and amplitudes.

While the occipital 8-13 c./sec. (alpha) rhythm progressively increases in size and in anterior spread over the brain, the central areas show for a time—possibly maximally from the third to the fifth year, a high voltage widespread 4-6 c./sec. rhythm on both sides (theta rhythm). By the eighth to the tenth year the occipital rhythm has reached “dominance” over widespread postcentral areas and the central theta rhythm is much smaller. There is, however, great variability in this respect among normal children and no precise criteria of normality can be recognized for any age. Henry’s (1944) careful study showed that females tend to have faster alpha rhythms than males, that the 10 c./sec. normal alpha frequency is first reached by the 13-year-olds. These changes could not be related to the onset of puberty, nor to skeletal maturity, nor to the intelligence quotient. As age increases there is a tendency for less slow activity to occur in the central areas and for the frequency of this slow activity to increase. Again correlations with I.Q. and skeletal maturity, when chronological age was held constant, were negative for the slow wave activity. Fast activity (more than 14 c./sec.), called beta rhythm, is uncommon in normal children under 14 years of age, but is more frequently seen in females than males.

It is at present quite uncertain when the adult pattern of EEG. is reached, and when no further changes can be anticipated. This event, which is almost certainly a variable between subjects is generally regarded as at some time between 18 and 20 years, but in many is certainly reached sooner and in some may occur within the third decade of life. As is well known, some 10 per cent of the population do not acquire patterns within the normal range, but it is still uncertain whether these anomalies are due to “maturational” defect or to unrecognized injury or disease.

Individual differences. During the greater part of adult life, at least until the age of 65, once the EEG. patterns have become stabilized, they remain invariable during the waking hours. The frequency of the alpha rhythm may vary from moment to moment by 1 c./sec. but this variability is itself a constant characteristic. The anterior spread, the presence of higher harmonics of the alpha frequency, any slight asymmetry on the two hemispheres and the presence or absence of fast rhythm in the precentral areas, remain unchanged. However, these characteristics which may distinguish one individual from another, disappear during sleep (Henry, 1941). The similar character of the patterns in identical twins provides good evidence of the genetic determination of the

main patterns. Attempts to relate such EEG. differences to differences in physique, intelligence or temperament have in the main failed. Golla, Hutton and Walter (1943) described a relationship between the persistence or absence of the alpha rhythm, the response of the rhythm to visual attention, and the main type of imagery, visual or kinæsthetic, used by the individual. According to this work, persistent unresponsive alpha rhythm is associated with lack of visual imagery and persistent absence of this rhythm with good visual imagery. Early attempts to relate such differences to the introversion—extraversion polarities of temperament have not been upheld (Henry and Knott, 1941). Some interesting relationships between alpha rhythm dominance and “active” or “passive” trends of the Freudian typology reported in 1937 by Saul, Davis and Davis, have been further supported by later study (1949). The problem of significance of individual differences is made more difficult of solution by the subtle alterations in basic EEG. characters which are now recognized to occur in states of fatigue, inattention, apprehension or fear and the now recognized effects of blood sugar variation and those of drugs which act upon the C.N.S.

Analysis of the Human EEG.

The most prominent rhythm which can be recorded from a pair of electrodes placed on the scalp is the 8–13 c./sec. activity first observed by Berger and later called by him alpha rhythm. This rhythm is largest in the postcentral areas of the head and its functions are related to those of the visual system. Another rhythm, maximal in precentral areas and also described by Berger, is smaller and faster, with a frequency of more than 14 c./sec.—usually about 22 c./sec., which is called *beta rhythm*. To visual inspection with the unaided eye, these two rhythms constitute the only phenomena of the waking EEG. in the majority of normal subjects, but in states of drowsiness or sleep, in childhood and senility, with variation in the chemical state of the cerebral blood, slower rhythms than the alpha may appear. In America, all such slower activity has been called *delta rhythm*, a designation first suggested by Grey Walter. However, the latter later suggested a division of the slower activity into delta rhythm (less than 4 c./sec.) and *theta rhythm* (4–7 c./sec.)—a division which has been largely adhered to by workers in Great Britain. The reasons for this division of the slower rhythm was found in certain physiological and topographical peculiarities which are believed to be associated with theta rhythm.

While in the majority of normal adults, the main rhythms, their frequencies and relative amplitudes, can be identified by visual inspection, the extreme complexity of different rhythms which characterize the EEGs. of children and the abnormal EEGs. of some adults, defy analysis by the unaided eye which is a poor analyser. Smaller rhythms are hidden by larger and slower ones ("masking"), whose wave-form they may distort. The appearances of the complex record depend upon the relative amplitudes, the relative frequencies and varying phase relations of the rhythms of which it is composed. To aid in sorting out the various components methods of automatic frequency analysis have been devised notably by Loomis, Harvey and Hobart (1936), Grass and Gibbs (1938) and by Grey Walter (1943). Standard manufactured apparatus of the latter type is now available. In this analysis the amplified output of the activity from the pair of electrodes to be analysed is presented to 24 electrical oscillators, each tuned to a particular frequency within the range of relevant frequency. The range of frequency of the tuned oscillators varies from 1.5 to 30 c./sec. and is suitably divided so that delta, theta, alpha and beta rhythms are represented. Associated with each tuned oscillating circuit is a storage device in the form of a condenser which receives a charge whenever a wave of the frequency to which the oscillator is tuned occurs in the output of the EEG. After a ten-second epoch, the whole oscillator system is automatically switched to a second and similar set of storage condensers, and the first set is discharged—each condenser in turn from the slowest frequency first, by means of a scanning switch. The relative charges on the condensers are "written out" in the form of a histogram over the primary EEG. trace. This process of "writing out" is arranged to take ten seconds after which the two banks of condenser are again changed over. The Walter method of automatic analysis, like the other methods so far devised, gives an accurate account of the various frequencies occurring in the EEG. record, but cannot describe the phase relations between the various components. The wave form and the appearances of the EEG. trace cannot therefore be predicted from the analyser histogram. Automatic analysis of frequencies must therefore never be divorced from inspection of the primary records.

Location of potentials. The location of the site on the head where the potentials which make up a rhythm have their largest size, which is the point of their origin, is of the greatest importance. In practice, three possible alternatives present.

1. A single point on the surface of the convexity of the head, from which the potential is greater with reference to any other point on the head, than the potential recorded from any two other points *equally spaced*. This is the case of the focus on or near the cortex.
2. Any two points, one on either hemisphere, but over similar homologous areas on the two sides, becoming equally positive or negative at the same time to any two other points on their respective hemispheres. In this case, that of the bilaterally synchronous rhythm, any two homologous points, one on either hemisphere, behave in a similar manner electrically at any one moment. In this event there is no single cortical or near-cortical focus and the activity is probably paced, as already indicated, by structures in the thalamus or deeper.
3. Potentials may be recorded from one hemisphere only and possibly from only one part of the head, but no single point of maximal potential can be constantly observed. In this case, no cortical or near-cortical focus can be found, and the phenomena are spoken of *lateralized* to the area of hemisphere concerned.

Two methods are in common use for the location of potentials. In both a number of equally spaced electrodes are arranged according to a standard plan on the two sides of the head. In the *unipolar* method the potentials recorded between the several electrodes on the scalp and an allegedly *indifferent* one, usually attached to the ear lobe, are compared. This assumes that the ear lobe electrode is truly "indifferent", that is, not near to active brain, which may not be the case for sources in the temporal lobe. Location is made by comparing the sizes of the potentials in the different channels.

The bipolar method was first devised by Adrian and Matthews (1934b) to locate the focus of the alpha rhythm. In this the potentials are recorded from pairs of "active" electrodes placed on the scalp, but the amplifiers are connected in series at common electrodes. When the focus of potentials lies beneath or near to such an electrode common to two series-connected amplifiers, the recording pens record the potentials out of phase in the two traces. If the other electrodes are equidistant to the common one, the potentials will be of equal amplitude.

Alpha rhythm reaches the adult frequency by the thirteenth year, but is often large in 9-10-year-old children. The frequency range is 8-13 c./sec., the amplitude 50-100 μ v through the intact scalp and skull. The commonest frequency is 9-10 c./sec. This

rhythm is dominant in the postcentral areas of the head, is fairly symmetrical on the two sides, and has a focus on either hemisphere in the visual association areas—the Vogt's area 19. It is often larger and more widespread on the right side in young persons, but in most subjects the frequency, persistence and the fluctuations of amplitude are symmetrical on the two sides. The origin of this rhythm and its relation to the activity in the thalamus has already been discussed (p. 180). Its appearance is evidence of physiological rest in the visual mechanism and its disappearance and replacement by rapid low voltage activity on attending to visual events or to visual imagery is characteristic. This response is sometimes termed the "blocking response" of the alpha rhythm. The early view that the disappearance of the alpha rhythm from the visual association cortex in the "blocking response" is due to the arrival at the cortex of an influx of asynchronous impulses up sensory projection pathways, which break up the synchronized autonomous beat of the cortical neurones, is no longer tenable in its original form (Jasper, 1949).

Jasper observes that the alpha rhythm is blocked in cortical areas far removed from the direct projection areas for afferent impulses. It was recognized very early in these studies that it was not the sensory stimulation itself but *attention to it* which caused the alpha rhythm to disappear. Jasper and Shagass (1941) showed that the blocking response could be conditioned to a sound stimulus. Further, the rhythm may block many seconds after the end of a sound stimulus if in preceding trials a light was presented after the same interval of time following a sound. This delayed effect could not be dependent upon the arrival of sensory impulses up primary projection pathways, but was dependent upon a conditioning process.

Morruzi and Magoun (1949) have demonstrated in animals that this blocking response can be produced by stimulation of the reticular formation of the brain stem. They obtained similar results from stimulation of the medial bulbar reticular formation, pontile and midbrain tegmentum, dorsal hypothalamus and subthalamus. Similar effects upon dial bursts of the cortex of the cat were observed from stimulation of hypothalamic areas by Morison, Finley and Lothrop (1943), Dempsey and Morison (1943), Murphy and Gellhorn (1945). More recently, Monnier (1949) has shown that alpha rhythm blocking is not initiated for a considerable period after the cortical electrical responses to the afferent volley are completed. This long latency suggests that some subsidiary

mechanism involving deep neurone systems may be involved in the blocking response. Moruzzi and Magoun (1949) postulate that collaterals from sensory paths first activate the brain-stem reticular formation and exert their influence upon the EEG. indirectly through it. However, the evidence that the reticular formation is involved in the blocking response of the alpha rhythm and the arousal reaction in man has not yet been obtained.

Beta rhythm is a normal low voltage activity seen in the pre-central regions on both hemispheres in normal adults. The frequency range is from 14-30 c./sec., the commonest frequency being 22 c./sec. Jasper and Penfield (1949) from human electrocorticography have demonstrated that beta rhythm is a specific activity of the motor cortex, the rhythm blocking selectively when movements are initiated or stopped from an area under observation. The initiation of movements of the fingers, for example, blocks beta rhythm in the hand area of the appropriate hemisphere, not in the face or leg areas. This activity is greatly increased during the early stages of sleep when it appears as "spindles". The dependence of this activity upon the integrity of deep structures was demonstrated by Henriksen, Grossman and Merlis (1949) in a patient with thalamic syndrome. During second induced sleep, in which the spindles of fast activity are normally very prominent, these were much reduced on the side of the thalamic lesion.

Theta rhythm is a normal activity in the child's EEG. and at any age during the early stage of sleep. Theta rhythm tends to be largest in the temporal and central areas of the cortex and has a frequency range from 4-7 c./sec. In the normal subject the activity is bilateral and symmetrical in occurrence. It seems probable that this activity is part of that functional system already described by which the thalamic reticular areas influence the cortex by diffuse projection. In the cat this activity can be induced by stimulation of this system in the thalamus. Theta activity is not influenced by sensory stimulation but is greatest in states of inattention and relaxation. Walter (1950) claims that theta activity can be increased by withdrawal of pleasurable stimuli in some subjects. Theta activity appears to be related to emotional states, is seen in excess in many patients suffering from psychiatric disorders, particularly those in which the personality is abnormally aggressive (Hill and Watterson, 1942). Theta activity is particularly prominent in patients suffering from space-occupying lesions

in the neighbourhood of the third ventricle (Cobb, 1945; Walter and Dovey, 1944).

Delta rhythm. While alpha, beta and theta rhythms are generally believed to be associated with certain cerebral areas, delta rhythm is designated by frequency only—a rhythm of less than 4 c./sec. Although this can occur as an abnormality anywhere on the head, in those conditions in which it appears as a response to some chemical change, the rhythm is seen usually in the pre-frontal areas first. Delta rhythm does not occur in the EEGs. of normal waking adults, but is seen during early childhood, in sleep, and in a variety of conditions in which the oxidation mechanisms or the acid-base mechanisms of the brain are altered.

Variation of the EEG. with Chemical Changes

Although the above description has divided the range of frequencies encountered in the EEG. into a number of discrete rhythms, each having a limited frequency range and some topographical location, it should be appreciated that this is done for the purpose of simplification. The EEG. of any part of the head, is in fact made up of a complex mixture of rhythms of frequencies often extending throughout the range of the whole spectrum. What can be counted by the unaided eye in any area is usually on the dominant frequency, which being the largest *masks* waves of lower voltage. Automatic analysis demonstrates this. All factors which deprive the cortex of oxygen slow the dominant frequencies of the EEG. while when the oxygen supply is increased, the dominant frequency increases. This has been shown by a number of workers in the case of oxygen deprivation in man (Davis, Davis and Thompson, 1938; Gibbs, Williams and Gibbs, 1940). In cardiac failure slowing of the rhythms is seen during the apnoëic phase of Cheyne-Stokes' respiration (Engel and Romano, 1944). These workers have also observed some slowing in patients with severe anæmia. Non-utilization of oxygen, as occurs in hypoglycæmia, results in gross slow wave activity at a time when the patient is still conscious, in contrast to the changes during oxygen deprivation when the appearance of slow activity coincides with loss of consciousness.

In clinical electroencephalography voluntary overbreathing is used as a routine to induce epileptic activity and to accentuate asymmetrical abnormalities. In all subjects there is a tendency for slight slowing and increase in amplitude of the rhythms to occur. This tendency is greatly increased by fasting the subject

or by inducing hypoglycæmia with insulin. The most important factor determining the degree of change is the age of the subject, gross changes occurring in most children when fasting. In normal adults over 40 little change in the rhythms is seen on visual inspection. In children and in abnormal adults, voluntary over-breathing may result in the replacement of normal rhythms by high voltage bilateral 3 c./sec. delta rhythm. The work of Gibbs *et al.* (1942) suggested that delta activity appears when the normal vasoconstrictor mechanism, serving to conserve CO_2 in the tissues, fails.

Darrow and his associates (1944a, b) demonstrated an important factor in the parasympathetic supply of cerebral vessels and postulated a complex theory to fit in with that of Gibbs. This theory postulates that no delta rhythm appears in the EEG. when the vasoconstrictor mechanism is inadequate unless the cholinergic and vasodilator action of parasympathetic impulses also fails. The latter, according to Darrow, is a second mechanism preventing excessive vasoconstriction which when it occurs locally, is responsible for the slow wave activity. Considerable experimental evidence in support of both theories has been produced.

Effect of Drugs on the Electroencephalogram

An extensive literature now exists demonstrating the effects of drugs on the electrical activity of nervous tissue and more on the ECoG. than the EEG. Reference will only be made here to those of relevance to human electroencephalography. Detailed consideration of this large subject has been given by Greville and Heppinstall (1950). In general, the convulsant drugs produce no changes with doses below the convulsant levels; this does not of course apply when such drugs are applied direct to the cortex. Slight increase in frequency can be observed after the administration of such C.N.S. stimulants as caffeine and to a certain extent after the sympathomimetic drugs, adrenalin, amphetamine and ephedrine. With clinical doses, little change is seen after atropine and hyoscine, but the former tends to reduce the number of spike and wave outbursts in the EEGs. of petit mal patients (Williams and Russell, 1941). With anæsthetics which produce C.N.S. excitation before depression, such as ether, cocaine and some barbiturates, fast activity is seen first in the EEG. and is later replaced by slow activity—on the other hand, drugs which only depress C.N.S. functions such as morphine, pethidine and alcohol, slow the frequency of the EEG. rhythms without any preceding fast activity.

In all cases the degree of slowing of the cortical rhythms relates particularly to the degree of impairment of conscious awareness induced by the drug, rather than to any specific pharmacological structure which the drug may contain.

ACTH and cortisone. Pine, Engel and Schwartz (1951) and Friedlander and Rottger (1951) have examined the EEGs. of patients undergoing treatment with ACTH and cortisone. Pre-treatment abnormalities of the EEG. were encountered in some patients suffering from rheumatoid arthritis, lupus erythemstosus and periarteritis nodosa. Cortisone alone produced little change in the EEG., the only significant finding was a slight but definite increase in the alpha frequency. Although no abnormal EEG. became normal as the result of cortisone therapy there was a general improvement in some cases. In 12 patients whose pre-treatment (cortisone and ACTH) EEGs. were abnormal, seven showed definite improvement in the record. Contrary to the findings of Hoefler and Glaser (1950) the EEG. did not develop slow waves as a result of ACTH therapy. When this occurs it is probable that the increased abnormality should be related to an advancing disease process. Unfortunately the converse does not appear to hold, since EEG. and clinical improvements are not related. It appears then that EEG. changes cannot be correlated in any direct way with the effects of adrenal hormone therapy. No relationship emerged between EEG. data and personality change, nor with other hormone effects such as electrolyte disturbance, eosinopenia, glycosuria, hyperglycæmia, hypertension, oedema or acne.

Psychological Relationships

In all conditions of the organism, normal or abnormal, physiological or pathological, the one significant relationship between the pattern of EEG. and the psychological state is that between frequency and the level of consciousness. An increase of the dominant frequencies of all areas is associated with increased alertness and attention (an exception is the case of barbiturates), a decrease with somnolence and inattention. In the depths of sleep the EEG. becomes very slow and this is observed in coma and delirium from any cause either intracerebral or systemic in origin. Engel *et al.* (1944) studied this relationship in patients in the wards of a general hospital, suffering from a variety of systemic diseases, which resulted in some alteration in cerebral metabolism, either by poor cerebral circulation, toxæmia or metabolic dysfunction. They described five stages of EEG. deterioration and related

these to degrees of impairment of conscious awareness. The latter was examined by a battery of cognitive psychometric tests, involving attention, recent memory, calculating ability, and the like.

Intellectual deterioration. EEG. patterns do not relate to irreversible deterioration in cognitive ability. Most demented patients (senile or arteriosclerotic), whose dementia is not dependent upon either a tumour or a rapidly developing cerebral disease to which a tissue reaction involving œdema is called out, have normal EEGs. Again however, the factor of impairment of consciousness is relevant. However, in some chronic epileptics, in some patients with chronic space occupying lesions (not located by the EEG.) and in some others who have passed through a prolonged and severe systemic illness interfering with cerebral metabolism for many months, the alpha frequency may be permanently slowed as a result. The alpha frequency in these cases is usually at 6-8 c./sec., symmetrical, but blocks rather poorly to arousal stimuli; the EEG. is otherwise normal.

Emotion. The anxious apprehensive subject usually shows a low voltage alpha rhythm, and a low alpha index (percent time alpha rhythm) compared with the relaxed subject. Lindsley (1951) has shown that the blocking of the alpha rhythm to a stimulus producing surprise, tension or apprehension is of longer duration than that to a more neutral stimulus. In both cases the latency time was the same, 0.4 second after the stimulus. The galvanic skin response follows after an interval of 1.5 seconds. It has been known for some years that great variability is to be witnessed in blocking latency time, both between individuals and on different occasions for the same individual. The mental set, or readiness to respond is probably involved here, the latency being shorter when the readiness to respond is greatest. Cohn (1946) describes two types of EEG. pattern in patients suffering from anxiety. In the first there is little alpha activity, but low amplitude beta rhythm; in the second there is an excess of high voltage fast rhythm together with predominant alpha rhythm. In the first type the patient is tense and the arousal mechanism (see p. 189) is presumably fully activated by cortical and hypothalamic impulses. In this type the EEG. becomes more normal when the subject is distracted, relaxed, or made to hyperventilate. In the second type of EEG. pattern the anxiety is witnessed in increased emotional behaviour and in autonomic disturbance.

Theta rhythm has been associated with emotional activity by a number of workers. Walter (1950) found that it was possible to

induce bursts of this activity by depriving young children of pleasurable stimuli—(sweets suddenly removed from the mouth). The writer has provoked bursts of theta rhythm by the presentation of psychological material carrying a high emotional charge to psychiatric patients, but only when these responses were already facilitated by hypoglycæmia. Mundy-Castle (1951) found an increased incidence of theta rhythm when subjects were embarrassed, frustrated or discomfited during the carrying out of mental tasks. This effect, as Walter and Walter (1949) and Mundy-Castle (1951) have shown can be greatly augmented by photic stimulation, the stimulus-frequency not being that of theta rhythm. In these experiments the photic stimulation is felt to be extremely unpleasant. Barker *et al.* (1950) reported that the EEGs. of some epileptics show bursts of spike and wave activity during interviews when unpleasant or threatening situations are discussed.

Personality. In a previous section it has been emphasized that no features of the developing EEG. relate to differences of intelligence. This is also true of the record of the mature individual if I.Qs. are considered. Further reference to the relationships between personality and the EEG. will be found in the section on Individual Differences (p. 185) and in a later section on Personality Disorder (p. 224). There is some evidence that within the normal population, slight differences can be found between the EEGs. of groups of persons whose personalities lead them to successful adaptation compared with those in whom adaptation is less successful. As far as individual prognostication is concerned these differences are, of course, of no value, since they are only demonstrable when the findings from two groups of persons are treated statistically. Much the same applies to investigations related to sex and race differences (Mundy-Castle *et al.*, 1953).

Intracranial Space-Occupying Lesions

Principles. From the point of view of electroencephalographic technique all space-occupying lesions can be considered together. Wave-form and frequency differences do not in any way reflect differences of pathological process. Whether the EEG. is abnormal depends upon:—

- (a) the site of the lesion.
- (b) the malignancy of the lesion, i.e. the extent to which the surrounding nerve tissue is disturbed by the lesion.
- (c) whether there is an increased intraventricular pressure.
- (d) whether the lesion is epileptogenic.

These points will now be considered.

Site. *Extracerebral lesions:* e.g. meningiomas, pituitary tumours, neurofibromas, subdural or extradural hæmatomas, do not change the spontaneous activity of the cortex unless the mass intervenes between the recording electrode and the brain and so constitutes a low-resistance pathway between electrodes. This may happen in large meningiomas, and subdural collections of blood particularly. The lesion is then recognized by a "silent" area. From this it follows that even massive benign lesions near a frontal pole, where there is little spontaneous activity in the cortex may be associated with a normal EEG., whereas lesions superficial to the postcentral cortex, where spontaneous activity is prominent, are more easily seen. Pituitary tumours and meningiomas arising from the base of the skull do not alter the EEG. until they interfere significantly with cerebral function.

Intracerebral lesions. Lesions of the brain tissue itself, if massive enough, may again be recognized by the fact that new tissue, inflammatory, neoplastic or degenerative, does not itself generate spontaneous activity and therefore if replacing normal cortex, be recognized also by a "silent" area from electrodes placed over them. Intracerebral lesions, particularly gliomatous, in the depths of a hemisphere may, however, slow the alpha frequency on the side of the lesion. Cerebellar masses cannot be localized directly by the EEG. and no change may be apparent until there is a rise in intraventricular pressure. The difficulties of identifying lesions increases progressively as the site of the lesion lies progressively further down the neuraxis from the cerebral cortex. Lesions situated in or near to the cerebral cortex, if they interfere with surrounding brain metabolism (see malignancy), generate activity in the delta range (less than 4 c./sec.) and the waveform is usually *irregular*, while lesions of the thalamus and neighbourhood of the 3rd ventricle tend to produce an excess of theta rhythm (4-7 c./sec.) in the fronto-temporal cortex. Cobb (1945) has found that lesions situated posteriorly near to the free margin of the tentorium may result in bilateral rhythmic 3 c./sec. at the vertex.

Malignancy. Slow wave activity is generated by live neurones whose metabolism is disturbed by pressure, by œdema, by toxins or by interference with their blood supply. Moreover when an area of cerebral cortex is functionally isolated from other areas or from deep grey matter by a lesion, rhythmic slow wave activity tends to appear from it. These factors of metabolic dysfunction and functional isolation occur most readily in rapidly expanding

lesions or very "malignant" lesions such as acute abscess, acute intracerebral hæmatoma, and malignant glioma. The thrombosis of a large vessel may produce comparable EEG. effects, but these subside within a very short time—a few days, compared with other types of lesions. Clearly a series of EEG. examinations after an acute cerebral catastrophe will enable the investigator to distinguish a purely vascular accident from the presence of a neoplasm. Benign lesions, for example, cysts of all kinds, even an entirely atrophic hemisphere do not of themselves generate abnormal potentials, but may be identified if the alpha-producing cortex is destroyed. The situation is of course different if the pathological process has resulted in the development of epileptogenic foci. The more "malignant" the process, in terms of interference with and destruction of surrounding brain, the greater the slowing of the spontaneous activity, which in the case of acute abscess, acute extradural hæmatoma (middle meningeal hæmorrhage) and rapidly developing glioma may be less than 10 per sec. and of great voltage.

Raised intracranial pressure. A general rise in intracranial pressure, even with gross papilloedema, does not alter the EEG. From animal experiments (Forster and Nims, 1942) the EEG. does not change until the I.C.P. rises above the blood pressure, when spontaneous activity ceases. When, however, the intraventricular pressure rises differentially, gross changes occur in the EEG., provided the process is fairly rapid (Williams, 1939). Normal rhythms disappear in all areas and are replaced by very slow (delta) irregular activity. This is called the "pressure record". When this situation, due it is supposed to oedema in the periventricular white matter, is caused by a lesion in the cerebral hemisphere, an intravenous injection of 50 c.c. of 50 per cent sucrose or other hypertonic solution, may result in temporary disappearance of the "pressure" patterns, but leave the focus of the lesion unchanged.

Special Cases. Secondary deposits. These present no special features except that the degree of abnormality they produce is usually not great, and when the lesions are multiple, the EEG. may be very complex with multiple foci.

Cysticerci usually produce no EEG. change and can rarely be identified by the technique.

Basal aneurysm. The EEG. is usually normal in cases of aneurysm, but after hæmorrhage into the brain tissue, lateralization of the lesion may be readily made. Millar (1953) examined 26 patients suffering from subarachnoid hæmorrhage, in 15 of

whom this had been due to a proven ruptured congenital aneurysm. In 13 the EEG. lateralized the bleeding point.

Subdural hæmatoma. The pattern may be very complex and deceptive. Sullivan, Abbott and Schwab (1951) reported on 32 cases, 24 being unilateral, four bilateral hæmatomas and four unilateral hydromas. Correct lateralization was made in 75 per cent of cases and a correct location in 47 per cent. Suppression of the alpha rhythm behind the hæmatoma was common and irregular continuous slow activity of low or moderate voltage occurred usually at the site of the lesion, only rarely on both sides. The EEG. did not distinguish between unilateral and bilateral hæmatomas and in two of the four patients with hydroma the EEG. was normal. Friedlander (1951) found EEG. abnormality in 92 per cent of 39 cases of subdura hæmatoma and made a correct location in 67 per cent.

Parasagittal lesions. Parasagittal meningiomas and small gliomas on the medial surface of the hemisphere are often not reflected in the EEG. patterns or give false localizing signs. Tükel and Jasper (1952) studied 31 cases of parasagittal lesions, seven of which were neoplasms, but all resulting in epilepsy. This study indicates that anomalous forms of spike and wave activity although bilaterally synchronous and not very dissimilar to the 3 c./sec. complexes of "idiopathic" petit mal may enable a location of such lesions to be made.

Tumours in the posterior fossa. It has already been noted that cerebellar tumours cannot be directly located by the EEG. The presence of an irregular focal slow wave disturbance from the cerebral cortex is however good evidence *against* a posterior fossa lesion in a doubtful case (Pampiglione, 1953). Cobb (1945) found rhythmic bilaterally synchronous slow waves when the lesion distorted the tentorium. Daly *et al.* (1953) confirm this finding in a larger series of patients in whom the lesions lay on the posterior fossa. This slow wave activity tends to be increased by overbreathing and to be blocked by arousal stimuli. Increased pressure within the 3rd and lateral ventricles, particularly when the rise in pressure is an acute rather than a slow increase, is of major importance.

Relationship Between Wave Form and Lesion

While there is certainly no specific relationship between the character of the waves at a focus of abnormality and the type of pathological process, it is clear, as already indicated, that acute

lesions of all kinds produce *irregular* high voltage slow activity. These focal disorders must be distinguished from the more *regular* rhythmic focal slow waves associated with more benign and chronic epileptogenic lesions. Spikes are rarely seen in association with acute lesions. In a series of 100 verified supratentorial tumours Kershman, Conde and Gibson (1949) found that focal slow waves at 1-3 c./sec. were most frequent in glioblastoma multiforme, less frequent in meningiomas and least frequent in astrocytomas. Focal 1-2 c./sec. waves were found in 92 per cent of glioblastomas. On the other hand focal sharp waves and focal spikes were common in astrocytomas. Seizures were commonly suffered by these patients (71 per cent) and this compared with the incidence of focal spike or sharp wave activity (61 per cent). On the other hand while many patients with meningiomas showed spikes or sharp waves in the EEG., far fewer suffered from seizures. The presence of such EEG. abnormality at a focus in a suspected case of neoplasm, would then suggest a meningioma if no seizures have occurred. The findings of other workers are similar.

EEG. after Head Injury

Concussion and contusion. From animal experimental work it has been observed that concussion is associated with a cessation of the electrical activity of the whole cerebral cortex. Recovery is associated with the reappearance of rhythmic activity, at first very slow, but soon increasing in frequency until the normal rhythms are re-established (Williams and Denny-Brown, 1941). Human patients who suffer concussion show generalized slow waves in the EEG. for some minutes or hours, even when no abnormal signs can be detected in the nervous system (Dow *et al.*, 1944). When cerebral contusion has occurred the EEG. abnormality of slow activity may persist for weeks, months or years. During the process of recovery from cerebral contusion, at first the generalized slow activity disappears, the normal rhythms reappearing in undamaged areas; the largest and slowest waves persisting in the contused areas.

Post-traumatic states. In a large series of cases Williams (1941) showed that the persistence of EEG. abnormality can be related to the duration of post-traumatic amnesia. Skull fracture, scalp wound and the duration of anterograde amnesia do not affect the persistence of EEG. abnormality; on the other hand, penetrating injuries were almost invariably followed by focal EEG. abnormality. This finding would undoubtedly have had to

be modified had the follow-up study been longer. Williams considered that clinical improvement in the post-traumatic patient normally occurs *pari passu* with improvement in the EEG., and that if this is not the case, the prognosis for complete recovery becomes ominous. Most writers agree (Gibbs, Wegner and Gibbs, 1944) that in the majority of patients who have sustained head injuries the EEG. has ceased to improve after two years from the injury. In all but the severest injuries the incidence of EEG. abnormality has fallen to about 15 per cent, and in the severest cases to about 38 per cent after two years. After this period of time only the focal EEG. abnormality can be ascribed to a past head injury, since the incidence of generalized slow activity is that of the incidence of similar abnormality in the general population—a point of some medicolegal importance (Heppenstall and Hill, 1943).

EEG. in Encephalitis

In the acute stages of all the known forms of encephalitis the EEG. is grossly abnormal, usually showing an excess of bilateral high voltage slow activity. The presence of such high voltage generalized slow activity without gross defect of sensorium and without seizures in an acutely ill patient with cerebral symptoms must always suggest this diagnosis. In those cases with a subacute onset the EEG. may show shifting foci of abnormality, the record at any one time suggesting a space occupying lesion or a recent vascular accident. Only serial records will reveal the probable nature of the disease process (Ross, 1945; Gibbs and Gibbs, 1947). In the rare subacute sclerosing encephalitis (van Bogaert, 1945) the EEG. shows repeated bursts of high voltage rhythmic slow wave complexes separated by intervals of eight to ten seconds of relative electrical silence. Each complex burst of abnormal activity initiates a wave of involuntary movements and from their recognition the diagnosis can be made (Cobb and Hill, 1950).

EEG. in Degenerative Disorders

It is recalled that abnormal potentials are generated only by diseased or dying neurones, not by dead ones. Gross absence of neurone structure does not itself affect the EEG. In the chronic stages of most cerebral degenerations the EEG. is therefore unchanged by the process. However, occasions of vascular accident, mental confusion and epileptic fits are associated with changes in the pattern.

Cerebral lipidosis; (Tay-Sachs disease): Few reports of EEG. findings in this condition have appeared. The record is

usually grossly disordered (Cobb, Martin and Pampiglione, 1952; Rosenbaum and Stein, 1953). A common pattern was recognized in 12 child patients studied by Cobb *et al.* This consisted of the occurrence of random, usually generalized sharp transient potentials on a background of generalized slow waves. The transients often showed triphasic components. These authors consider that recognition of the pattern has definite diagnostic value, being quite different from that found in Schilder's disease and in other cases in which epilepsy and mental deficiency coexist. But this pattern was not found in two adult sufferers from cerebral lipidosis.

Schilder's disease: Gibbs and Gibbs (1941) and Williams and Gibbs (1939) showed EEGs. of cases of Schilder's disease with high voltage slow waves with associated small spikes. The diagnoses in these cases were not confirmed by autopsy. In the cases of Cobb *et al.* (1952) three who died of Schilder's disease diagnosed at autopsy, had shown no spikes or transient activity in their EEGs. despite the fact that fits had been a feature of their illnesses.

Hepato-lenticular degeneration (Wilson's disease): The EEG. is sometimes abnormal in this condition (Hill, 1948a; Stephens, 1951), but the patterns show no characteristic features.

Pernicious anaemia: A study of a large series of cases by Walton, Kiloh, Osselton and Farrall (1954) indicates that the EEG. is frequently abnormal in this condition (60 per cent pre-treatment cases), improves under treatment with vitamin B₁₂, usually within 10 to 30 days, but may continue to do so up to three years after treatment is commenced. Eventually over 80 per cent of cases showed a normal EEG.

Huntington's chorea: The EEG. of the established case of this condition is characteristically flat, that is, shows very little spontaneous activity. Progressive disappearance of rhythmic activity accompanies the deterioration of the patient. Attempts have been made to use the EEG. to predict which members of a family will later develop the disease (Patterson *et al.*, 1948; Harvald, 1951; Leese, Pond and Shields, 1952), since the EEG. is abnormal in a proportion of other siblings, but the findings are inconclusive.

Cerebral hemiatrophy of childhood (infantile hemiplegia): Areas of cortical atrophy show a reduced or absent alpha activity, but even a tissue-thin cerebral cortex, if live cells are present, can generate spontaneous activity. The EEG. may therefore be normal even with gross unilateral dilatation of the lateral ventricle. In

these cases, however, barbiturate-induced fast rhythm, which is normally symmetrical in appearance, fails to appear or is reduced on the damaged side (Pampiglione, 1952). Sleep, either natural or induced by a drug, can also be used to demonstrate unilateral atrophy, since the responses to arousal stimuli tend to be absent or reduced on the abnormal side. Many such cases, of course, suffer from fits and spike or sharp wave foci, either single or multiple may appear both on the abnormal and the normal sides of the brain. As Cobb and Pampiglione (1953) have shown, the presence of such epileptic activity on the normal cortex is not a contraindication to hemispherectomy of the atrophied side, since these secondary foci tend to disappear after the operation. After hemispherectomy the record from the normal side tends to improve, spike discharges to disappear and normal rhythms to be re-established. The apparent appearance of normal rhythms on the hemispherectomized side can be explained as physical spread from the remaining hemisphere. The greatest abnormality is seen in the youngest patients, and in those with early onset of the hemiplegia there is the greatest improvement in the EEG. after operation (Cobb and Pampiglione, 1952).

Presenile atrophy: In the majority of patients the EEG. is normal or shows only minor unspecific abnormality. During periods of mental confusion or when epileptic seizures occur, the EEG. becomes grossly abnormal (slow waves) or shows a focal abnormality reflecting the site of seizure onset and probably the most active area of disease process. Mengoli (1952) in a study of the EEG. of old age, found as others have done that there is increasing fast rhythm in the later years, but that in 25 per cent of patients between 60–93 years of age there is generalized slowing of the normal rhythms in some degree. In presenile dementia (patients aged 55–60 years) this slowing was more constantly found and was more severe, with disappearance of the alpha frequency.

The EEG. changes in patients suffering from cerebral arteriosclerosis are very similar, the majority showing normal patterns. The chief value of electroencephalography in patients of this age group presenting with dementia is the exclusion of tumour. A slow wave focal abnormality, particularly with *irregular* wave form should always suggest an expanding lesion.

Vascular Accidents

Cerebral thrombosis: For a period of days or a few weeks the EEG. shows local abnormality—depression of normal rhythm

and the presence of slow waves after thrombosis of one of the main cerebral vessels. After this initial period the EEG. returns to normal in the great majority of cases. Negrin (1951) found the severest and the most persistent abnormalities after thrombosis of the internal carotid artery. In these cases the alpha activity in the occipital areas was spared. Jones and Bagchi (1951) found that in thrombosis the EEG. abnormalities, often focal, are located to the areas of distribution of the affected vessel.

Cerebral hæmorrhage: Focal slow waves, appearing after hæmorrhage, disappear within days or weeks from the EEG. (subarachnoid hæmorrhage see p. 197).

Cerebral embolism: Zfass and Hoefler (1950) contrasted the focal EEG. abnormalities which occur after cerebral embolism with those after thrombosis or hæmorrhage. After embolism, focal EEG. abnormality tends to persist much longer—even up to a year, and after clinical improvement has occurred. The value of electroencephalography after unexplained cerebral catastrophes is undoubted if serial spaced records are taken. While the cerebral neoplasm is associated with the progressive development of abnormality, the EEG. after “pure” vascular accidents progressively improves and ultimately in most cases returns to normal.

Other cases: In the great majority of patients suffering from disseminated sclerosis, cerebral diplegia, and from conditions in which primary degeneration of tracts such as the heredo-familial ataxias (Friedreich), spastic paralysis, progressive muscular atrophy and amyotrophic lateral sclerosis, etc., the EEG. is normal. Schwab (1951) adds to this list myasthenia gravis, syringomyelia, the muscular dystrophies, myotonia congenita, and Parkinsonism.

EEG. in the Epilepsies

Electrophysiological Observations: (a) *Epilepsy of cortical onset.* The early studies of Adrian *et al.* (1934b), Moruzzi and Adrian (1939) showed that weak stimulation of an area of cerebral cortex produced an initial negativity close to the stimulated area which was attributed to the firing of neurones in the superficial cortical layers. Stronger and repeated stimulation produced a “deep response”, indicating activity in deeper cortical layers and this was associated with an outwardly spreading wave of potential, considered to be due to the activation of deep cortical neurones further and further away from the stimulated point. If this occurred from stimulation in the motor area of the monkey, movements in the contralateral limbs were witnessed which related to

the "deep response". Following the stimulation, if the latter was of sufficient intensity, grouped after-discharges were witnessed from the cortex and these correlated with clonic movements in the limbs. Erichson (1940) showed that spread of the after-discharge to the other hemisphere was via the corpus callosum, and if this was severed, contralateral clonic movements and ipsilateral tonic movements resulted. Rosenblueth and Cannon (1942) in a series of beautiful experiments on monkeys showed that the tonic and clonic electrical activity could occur in any normal area of cortex and spread to the motor cortex by intracortical routes. The EEG. of the tonic-clonic response showed that immediately after stimulation the record was silent. Then occurred short duration, rapid, thirty- to eighteen-per-second waves, increasing in amplitude and often showing "beats" of slow periods; then slower fifteen- to six-per-second waves; then irregular activity of larger amplitude with some fast "spike" and some slow components. These tended to organize as regular rhythmic patterns of progressively decreasing rate consisting of one or more spikes and a slow, large wave. The end of the abnormal discharge was sudden and was followed by a featureless EEG. with the original spontaneous activity decreased or absent. Spontaneous activity then reappeared and slowly grew to resting amplitude and frequency.

In the earlier stages, no close correlation was observed between the EEG. and records from the muscles. Later, the rhythmic pattern of cortical discharge was correlated in rate and amplitude with muscular contractions. The authors found that self-sustained cortical activity could be evoked without leading to any movements and also from any part of the exposed hemisphere. A wide spread of activity could also be produced, developing gradually but ceasing simultaneously and not attributable to any systematic pacer-maker. Direct stimulation of the striatum, thalamus and cerebellum, however, never led to self-sustained responses. The self-sustained repetitive discharges resulting from cortical stimulation were attributable to an intrinsic ability of some cortical elements to discharge rhythmically. The widespread synchronism revealed a system of nervous pathways interconnecting some elements in all cortical areas.

Hoefler and Pool (1943) showed that the cortical discharges during seizures resulted in conducted spike activity in bursts in the pyramidal tracts and was more continuous in extrapyramidal pathways within the reticular substance. Contrary to the work of Erichson (1940) and Rosenblueth and Cannon (1942) already cited,

Hoefer and Pool did not find that section of the corpus callosum prevented generalized tonic-clonic convulsions. The importance of the extrapyramidal pathways in the motor "exit" of the seizure discharge remains undecided.

(b) *Diencephalic mechanisms.* It is well known that in many patients the seizures do not start from a cortical focus and that the electrical activity of the seizure although seen as a series of cortical potential charges, is projected from deep brain structures. The physiological experimental work which formed the background to new knowledge in this field must be attributed to the series of remarkable observations made by Dempsey and Morison in 1941-1943. Reference to this has already been made (see p. 181). Jasper (1941) was the first to suggest that the bilaterally synchronous spike and wave activity of petit mal suggested a deep diencephalic origin. Hursh (1945) showed that section of the corpus callosum did not effect the bilateral synchrony of these discharges and hence the seizure spread could not be from cortex to cortex. Jasper and Fortuyn (1947) and Hunter and Jasper (1949) demonstrated that in the cat stimulation of the antero-medial thalamus with inserted electrodes resulted in both petit mal-like seizures in the freely moving animal and an electrocorticogram of bilaterally synchronous spike and wave activity. In the first investigation the areas of thalamus responsible for this type of response were limited to the intralaminar structures. If the intensity of the stimulation was increased the petit mal response turned into a grand mal i.e. a tonic clonic convulsion. The anatomical basis for the diffuse projection system of the intralaminar areas remains in doubt. It is possible, however, that the pathways lie through the association nuclei of the thalamus, which thus relay the responses to the projection areas (Starzl and Whitlock, 1952).

(c) *Centrencephalic integrating system.* This term was given by Penfield (1952) and includes not only the thalamic reticular system described above, but also the whole midbrain reticular system already described (p. 183). The arousal functions of the latter upon the cortex is probably mediated by activation of the thalamic system. The opposing nature of these two parts of the system is emphasized by the work of Moruzzi and Magoun (1949) who showed that the "recruiting response" of the cortex induced by low frequency stimulation of the intralaminar thalamic areas can be reduced or abolished by midbrain reticular stimulation. Thus a physiological basis for the early observation of Lennox, Gibbs and

Gibbs (1936) that the spike and wave sequences of petit mal can be arrested by an arousal stimulus, has been given. The experimental work to which these paragraphs have referred, which has such great importance for clinical medicine, forms an important contribution to what Purpura (1953) in an excellent review of this subject has called the "Golden Age of Neurophysiology".

Classification of the EEG. in Epilepsy

The first classification of Gibbs, Gibbs and Lennox (1938a) was based on visual appearances of wave form and frequency alone. Four types were recognized:—

- (1) Paroxysmal fast rhythm or spikes (grand mal phenomenon).
- (2) Three per second spike and waves (petit mal phenomenon).
- (3) Four per second square topped waves and 6 c./sec. rhythm (psychomotor phenomenon).
- (4) Slow spike and waves (petit mal variant).

Localization studies made this classification unsatisfactory since as soon as it was recognized that it was not possible to relate a specific wave form or frequency to a certain type or seizure pattern, the important issue was to identify the focus of origin for the abnormal discharge. Jasper (1949) demonstrated that a remarkable variety of wave forms can be recorded by electrocorticography from the neighbourhood of cortical lesions of all kinds. These wave forms included not only paroxysmal grouped or single spikes and long duration spikes (sharp waves) but also discharges of high voltage rhythm from 2 to 20 per second and focal slow spike and waves. Jasper considers that the following three questions should be answered when confronted by an EEG. of an epileptic. (1) Is there any evidence for a focal epileptogenic lesion of the cortex? (2) Are the paroxysmal discharges observed from the cortex *projected* from subcortical structures or systems, with no evidence of primary cortical abnormality? and (3) Is there any evidence for a diffuse cerebral disease probably affecting both cortical and subcortical structures? With these three questions in mind he constructed the following main groups of EEG. abnormalities.

- (1) Focal cortical.
- (2) Projected subcortical.
- (3) Diffuse dysrhythmias.

It will be observed that the idiopathic epilepsies (petit mal, petit mal and myoclonic jerks and grand mal, i.e. major convulsion without aura) fall *for the most part* into the subcortical projected group. Jasper (1949b) believes, however, that the EEG. alone cannot safely differentiate between idiopathic and symptomatic epilepsy since the same EEG. disturbance, e.g. subcortical projected phenomena, may be produced by certain organic lesions or diseases "affecting principally the same neuronal mechanisms involved in the idiopathic disorders". Moreover it is now evident that discharges of the subcortical projection type can be initiated by a cortical focus associated with a local lesion. These *secondary* subcortical projection discharges are particularly liable to occur in the case of (a) focal lesions in the infero-temporal cortex (uncus and hippocampus) and (b) focal lesions on the medial surface of the hemisphere. The 3 c./sec. wave and spike with *true* bilateral symmetry, and constant frequency for the complexes is probably always a true *primary* subcortical projected discharge. The methods of distinguishing primary and secondary projected discharges from subcortical areas have been outlined by Tükel and Jasper (1952).

Table I gives a classification of the main wave forms in epilepsy and this is illustrated in Figs. 20-22.

Special Cases

"Psychomotor epilepsy". Jasper (1941), Gibbs *et al.* (1947) and Hill (1949) recognized that the "squared topped" waves at four per second were indeed not rhythmic waves at this frequency, but monophasic sharp potentials (long duration spikes) repeating regularly. Such repeated spike discharges can occur from any epileptogenic focus on the cerebral cortex. Electroencephalography often shows runs of such discharges from silent areas of cortex without clinical accompaniment. The long duration of the spikes may be explained as due to temporal dispersion of the impulses composing the potentials. The dispersion is probably due to the varying number of synapses on the pathways between the recording electrodes and the source, and the monophasic character of the potentials, an artefact of the recording technique. They are seen as monophasic much more clearly with monopolar leads referring to an "indifferent" point than with bipolar leads (see p.-188). When the activity from such a cortical focus is conducted to subcortical structures, the subcortical projection system of the thalamus may be activated, consciousness is lost and this is associated with bilateral recruiting slow activity on both

sides of the cortex. Starting with low voltage 6–8 c./sec. activity, discharge becomes progressively larger and slower, ending the after a variable period of one to two minutes at about 2 c./sec.

TABLE I

(Adapted from Jasper and Kershman, 1949)

<i>EEG. Group</i>	<i>Wave Forms</i>	<i>Type of Pathology</i>
1. Focal cortical Paroxysmal discharge consistently localized to a single focus. (a) <i>small superficial focus</i> (b) <i>superficial epileptogenic area</i> (c) <i>buried focal lesion</i> (beneath cortical convexity)	<i>local sporadic spikes or sharp waves; slow waves; local paroxysmal rhythms; local spike and wave complexes</i> (a) sporadic spikes (10–40 c./sec.) with spike and wave sequences, multiple spikes at onset of attack. Normal background activity. (b) paroxysmal sharp waves 50–500 c./sec. with slow delta activity widespread. (c) secondary conducted sharp waves or secondary projected rhythms, often bilateral. (Primary focus demonstrated by special leads—pharyngeal, sphenoidal, etc.)	porencephaly atrophy meningo-cortical cicatrix scar, neoplasm atrophy neoplasm (rare) atrophy gliosis
2. Projected subcortical Primary projected rhythms, no cortical focus; interparoxysmal activity relatively normal	(a) 3 per second bilaterally synchronous wave and spike (b) multiple spikes and wave, irregular short bursts multiple spikes and waves, often bilaterally synchronous. (c) sharp and slow wave (slow spike and waves) widespread, paroxysmal, usually bilaterally synchronous rhythmic complexes at 2–2.5/sec., often irregular form—variable location on scalp. (d) paroxysmal fast rhythms bilateral generalized 7–10 c./sec., 11–15 c./sec., 16–30 c./sec. rhythm. (e) paroxysmal slow rhythms bursts of 2–6 c./sec. rhythm.	idiopathic petit mal and onset grand mal myoclonic epilepsy (? idiopathic) diffuse cerebral lesions focal brain stem lesion or combined with diffuse cerebral atrophy usually idiopathic usually idiopathic
3. Diffuse dysrhythmias Multiple, usually disorganized paroxysmal discharge, with continuous abnormality in interparoxysmal records	(a) high voltage slow generalized slow and sharp waves with no fixed frequencies. Multiple apparent foci may appear. Occasional slow wave and spike forms, with poor bilateral symmetry (b) low voltage amorphous, low voltage mixed fast and slow waves poorly organized or absent alpha. High voltage paroxysmal discharge on special provocation only.	diffuse encephalopathy, diffuse cortical atrophy no demonstrable pathology ? brain stem or diencephalic origin

FIGS. 20-22 ILLUSTRATE THE FORMS OF EPILEPTIC DISCHARGE CLASSIFIED IN TABLE I.

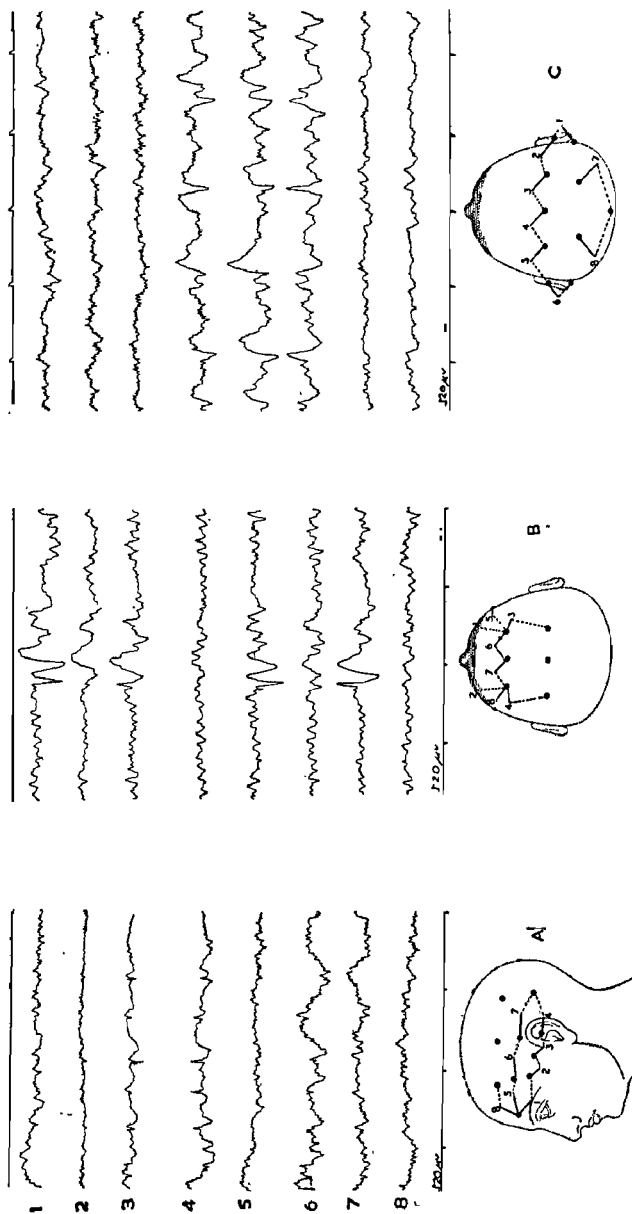


FIG. 20 shows three forms of focal cortical discharge.

- A. A small superficial focus of sporadic spikes, located to the ear electrode on the left side in channels 3 and 4. Little spread to other area is seen. Temporal lobe epilepsy with atrophic cortex.
- B. A superficial epileptogenic area, seen as paroxysmal sharp waves of high voltage, located in two planes of space to the right frontal electrode between channels 1 and 3, 5 and 7. Oligodendroglioma right frontal lobe; fits.
- C. A buried epileptogenic focus in left sylvian region seen as long duration sharp waves located at electrode between channels 5 and 6. Epilepsy with gliosis.

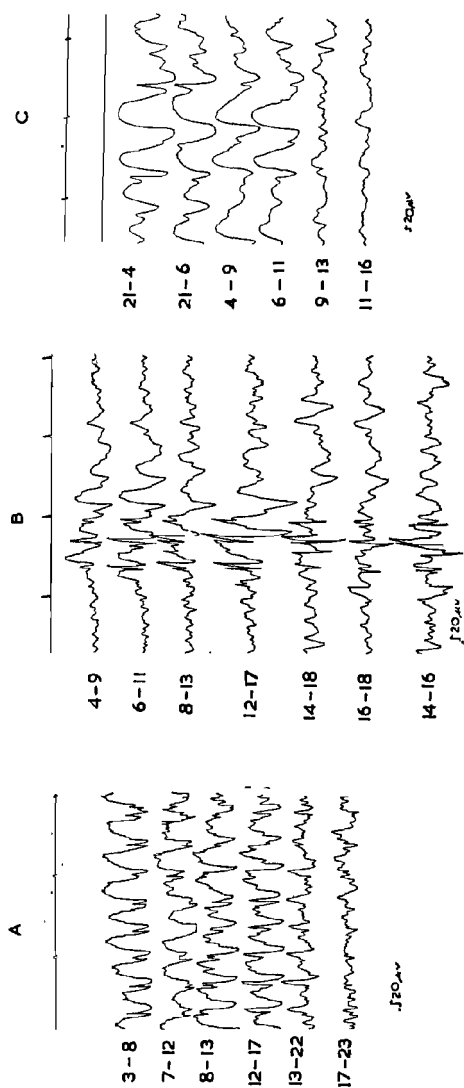


FIG. 21 illustrates the forms of projected subcortical epileptic activity.

- A. Three per second bilaterally synchronous wave and spike activity. Idiopathic petit mal.
- B. Multiple spikes and wave with tendency to bilateral synchrony. Degenerative myoclonic epilepsy.
- C. Paroxysmal sharp and slow waves (slow spike and waves) with bilateral synchrony. Epilepsy with deterioration.

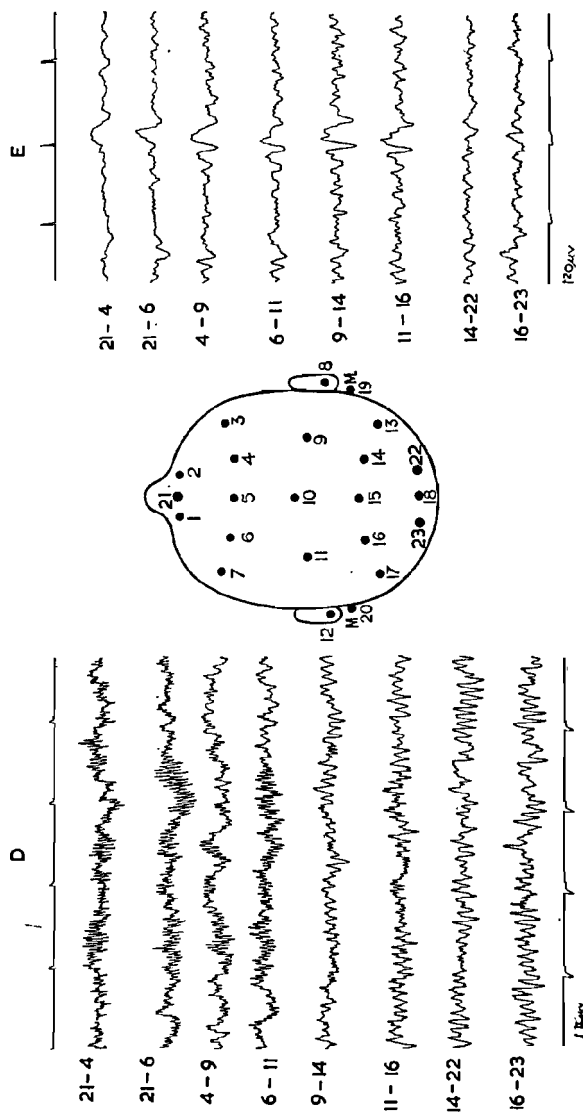


FIG. 21.

D. Paroxysmal bilateral fast rhythm. Epilepsy, non-specific.
 E. Paroxysmal bilateral slow rhythm. Epilepsy, non-specific.

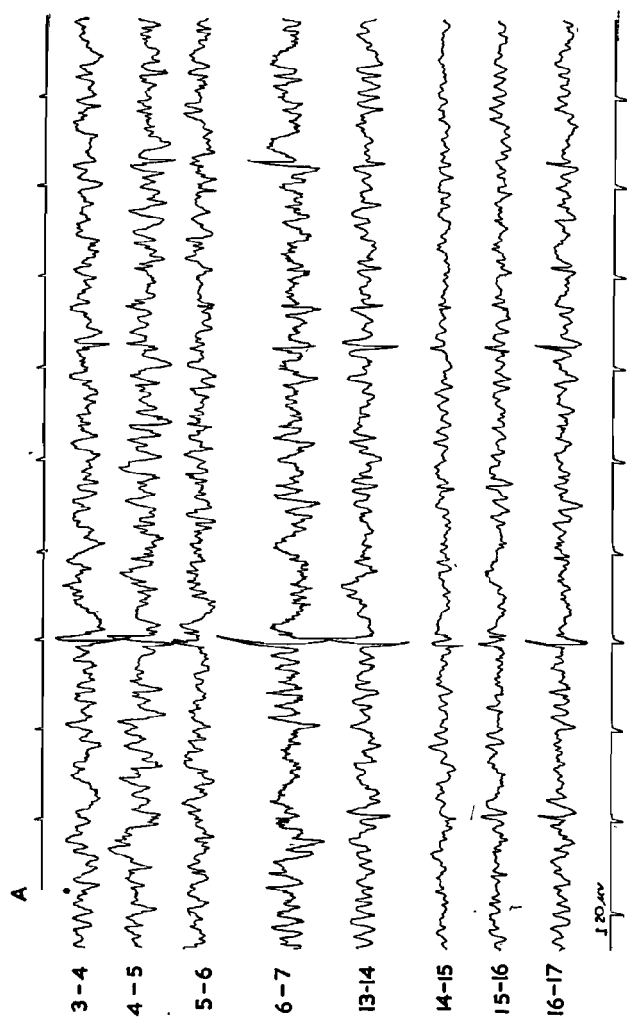


FIG. 22 illustrates the diffuse dysrhythmias.

A. Multiple spike foci and high voltage spikes with bilateral synchrony. Epilepsy with evidence of diffuse pathology.

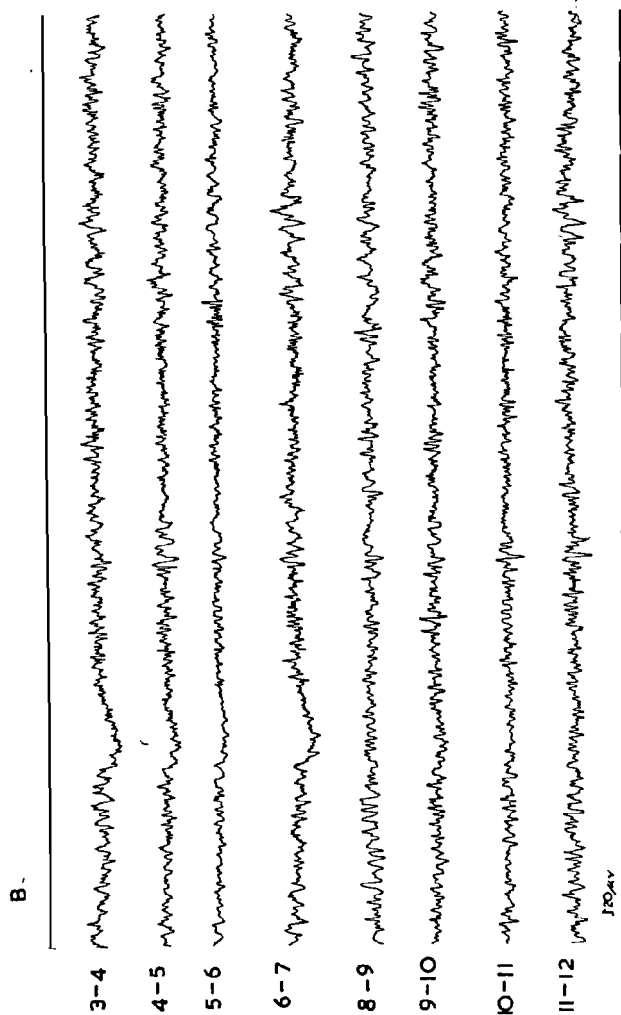


FIG. 22.

B. A low voltage record showing many frequencies, fast and slow but no alpha activity. Chronic psychosis without epilepsy. Aetiology obscure. (For electrode positions refer to Fig. 21.)

The postictal record is flat and featureless, but returns to normal pattern after 10–20 minutes. The discharge is very similar to the basic slow build-up of the subcortical projected major convulsion *without* the associated cortical spikes. The commonest site for the cortical spike focus which will readily initiate the subcortical projection system discharge is the deep grey matter of the temporal lobe—the uncus and the hippocampus. Because of the complex clinical aura of discharges in these areas, the most suitable term for epilepsy arising there or in the immediate neighbourhood of the temporal lobe would be “temporal lobe automatisms”, or “temporal lobe epilepsy” since an automatism is not the invariable accompaniment. It should be emphasized, however, that epileptic automatisms can be initiated by cortical epileptic foci *outside* the temporal lobe—frontal, parietal or from the medial and orbital surfaces of the brain. However, it is probable that about 90 per cent of patients suffering from automatisms have EEG. cortical foci in one or both temporal lobes, in their anterior part.

Temporal lobe epilepsy (psychomotor, psychic, uncinate, major convulsive seizures, *particularly nocturnal*). It is probable that about a third of all epileptics suffer from seizures starting from a focus in the temporal cortex or its deep structures—the uncus and hippocampus. The work of Penfield and Baldwin (1952) makes it probable that the majority of these are associated with a pathological process of some kind, birth trauma or anoxia being the commonest. Using the routine scalp electrodes, and examining the patient in the conscious state will only reveal the spike focus in a small proportion of cases. Natural sleep or narcosis induced by a barbiturate (Seconal grs. $\frac{3}{4}$ – $1\frac{1}{2}$ for a child; grs. 3 for an adult, or I.V. Pentothal) and the use of special electrodes (pharyngeal, sphenoidal, tympanic, etc.) reveals the discharging area in over 90 per cent of cases. When this type of technique fails on the first occasion, repeating it after an interval particularly if anticonvulsants are withdrawn is usually successful. Discharging foci in these brain areas can be classified as follows (Jasper, *et al.* 1951; Hill, 1953).

- (a) Spike foci in the depths of the Sylvian fissure seen as repeated long duration sharp waves from scalp.
- (b) Spike foci on the lateral surface of the temporal cortex
 - (i) anterior to and (ii) posterior to midzone (horizontal through external auditory meatus).
- (c) Spikes of short duration at sphenoidal electrode only.

- (d) Sharp waves at sphenoidal electrodes, seen equally at temporal convexity and/or frontal areas also.

Such epileptic foci can also be very usefully categorized as under.

- (1) Strictly unilateral.
- (2) Unilateral with spread to either inferior or lateral surface of contralateral temporal lobe.
- (3) Bilateral independent spike foci.
- (4) Bilateral synchronously firing spike foci either at inferior surface (sphenoidal electrode) or at convexity (rare).
- (5) Multiple independently firing foci on both sides.

The electroencephalographic differentiation of these possibilities is of first importance where surgery is contemplated and necessitates repeated examination. The ideal case for surgery has been found to be C(1), i.e. a strictly unilateral focus of spikes at the sphenoidal electrode only. Gastaut (1953) in an excellent review of this subject has given a tentative classification of psychomotor (temporal lobe) epilepsy based on the site of origin of the seizures and the mechanism by which they spread.

(a) **Temporal psychomotor epilepsy** or superficial temporal psychomotor epilepsy (rare). Spike focus found on the lateral surface of the lobe or inferior surface, excluding apex. (Lesion often of infective or vascular nature, e.g. otogenic infection.)

(b) **Hippocampal psychomotor epilepsy**. Unilateral or bilateral independent slow spikes widely distributed over temporal region of scalp (clear spike focus at sphenoidal electrode—author). (Commonest.) Lesions: birth trauma, ischaemic atrophy.

(c) **Diencephalic psychomotor epilepsy**. Widespread temporal and frontal spikes independently on the two sides of the brain. Discharges projected from diencephalic structures, where lesions lie, i.e. encephalitis.

Activation of the EEG. in epilepsy

Methods of activation of epileptic pattern in the EEG. of patients suspected of the condition have been elaborated in the last few years. These can be listed as follows:—

(a) **Voluntary overbreathing**, preferably in the fasting state, is most efficacious in the young subject and is more likely to elicit subcortical projected activity (i.e. spike and wave complexes) than a cortical spike focus. The method is also of value in the young subject to elicit asymmetries due to cortical atrophy.

(b) **Induced hypoglycæmia.** This method is time-consuming, the results are unpredictable and it has largely been abandoned for clinical purposes. Cortical spike foci and subcortical projection activity can both be elicited by the method.

(c) **Intermittent photic stimulation.** High intensity flashes of short duration, repeated at a frequency from 1 to 50 a second are now regularly used to elicit subcortical projected activity of epileptic type. The method was introduced by Walter *et al.* (1946) and has been elaborated and studied by many workers, notably Walter and Walter (1949) and Gastaut *et al.* (1950). The results, however, must be interpreted with caution. The normal responses, called "driving" or "following" of the rhythms of the postcentral cortex, can occur at the flash frequency or at subharmonic, or high harmonic frequencies of it. The different types of harmonic response, particularly if these are asymmetrical on the two hemispheres, may have clinical significance. Abnormal responses in the form of 3 c./sec. wave-and-spikes, multiple spikes, mixed spikes and waves with inconstant relationships and high voltage slow waves occur, the most sensitive frequency of flash being 15 to 18 per second. Bickford *et al.* (1952) have differentiated a prefrontal multiple spike response associated with clonic activity of the periorbital musculature and shown that this is not a response of the cerebral cortex, this type of response is common in tense, emotional subjects. There can be no doubt, however, that the abnormal responses, particularly the slow wave, multiple cortical spikes and mixed spikes and waves occur occasionally in normal subjects, and to a greater extent in neuropsychiatric patients, who have never suffered from a known epileptic seizure. The previous state of the subject and the presence of other stimuli may modify the responses (Pampiglione, 1952). A diagnosis of epilepsy should not therefore be made solely upon a positive response to photic stimulation.

(d) **Combined photic stimulation with intravenous metrazol.** The literature concerning this method, introduced by Gastaut (1950), is now extensive. The method has been standardised, the *photometrazol threshold* being the amount of metrazol in milligrams per kilo body weight required to produce the abnormal EEG. response, while flashing light at about 15 per second is presented. Since the clinical accompaniment of this cortical response is usually a series of muscular jerks, it has also been called the *myoclonic threshold*. This threshold for normal subjects of about 60 kg. is about 600 mg. metrazol injected at the rate of 50 mg. every

30 seconds, which is about 10 mg. per kilogram body weight (Gastaut, 1950). If further metrazol is injected or if the flickering light is left too long in front of the eyes, a seizure is likely to occur. The myoclonic threshold is therefore in many cases near to the convulsive threshold. The threshold is lower in epilepsy of the petit mal type (i.e. subcortical projection type) than in the grand mal type. (0.5–1.5 mg./kg. to 3–5 mg./kg. respectively). Gastaut also found a low threshold in some cases of hysteria and schizophrenia (see p. 224). In a study of non-epileptic psychiatric patients Leiberman, Hoenig and Hacker (1954) found a wide distribution of photometrazol thresholds, in fact a distribution curve almost approximating to "normal". While the method has great possibilities as a tool for exploring cerebral activity, it is agreed that it has little diagnostic value.

Mechanism of photic activation. Gastaut and Hunter (1950) showed that the EEG. pattern of "idiopathic" epilepsy is readily brought about in the experimental animal. It can be brought about without any trauma to cerebral structures by simply increasing the degree of excitability of these structures by chemical means (metrazol) and then bombarding them through their specific afferents. The normal responses to intermittent photic stimulation are limited to the geniculate bodies and the primary and secondary visual cortical areas. When the "threshold" is reached as a result of metrazol injection, the responses become irradiated to the thalamic nuclei and to other regions of the cortex where it may be localized to the frontoprecentral regions. Each response is accompanied by a myoclonic jerk of the limbs predominantly in flexion. This myoclonic element is not suppressed by the complete ablation or freezing of the precentral sensorimotor cortex. Similarly ablation, freezing or isolation of the visual cortex of one side does not suppress the irradiated response, nor the bilateral myoclonic jerks. Bilateral ablation, however, brings about a disappearance both of the irradiated response and the myoclonic jerks. The irradiated response would appear to be elaborated in the thalamus and "to result from an abnormal permeability of the thalamic synapses to the convergent action of impulses derived from the visual pathways". Tridione caused a disappearance of the irradiated response without affecting the primary visual area responses. Phenobarbitone in high concentrations caused a disappearance of both types of response. Gastaut and Hunter (1950) consider that the abnormal responses to photic stimulation (zero threshold)

and a low photo-metrazol threshold are indicators of the degree of "epileptic diathesis". To quote them—"The discharge of thalamic neurones which brings about this trend of events at a cortical level is itself set up by a propagation to the whole thalamic system of impulses which should never have spread. This is possibly mediated by the intralaminar system" (see p. 205).

(e) **Slow intravenous injection of metrazol.** A uniform technique for the slow intravenous injection of metrazol, allowing for body weight variability has been described by Jasper and Courtois (1953). This method is of value in the activation of the cortical spike focus in patients with focal cortical epileptic seizures. It is of less value in patients whose characteristic seizures are major convulsions, even when the aura indicates a focal cortical onset.

(f) **Sleep.** Gibbs *et al.* (1947) first demonstrated that epileptic discharges were commonly induced in the EEG. during natural sleep and reported an 82 per cent incidence of such discharges compared with 36 per cent while awake in 500 epileptic patients. Merlis *et al.* (1951) compared the use of natural or induced sleep (oral paraldehyde or seconal) and I.V. metrazol as activation methods. Sleep was most useful in patients with temporal lobe epilepsy. Metrazol proved of more value than sleep, inducing seizure discharges in 45 per cent of 77 patients with normal or borderline records while awake; sleep on the other hand was successful in only 13 per cent of the group. Metrazol was more effective than sleep in all clinical groups except in the temporal lobe epileptic group. In the latter the precise location of the focus was best demonstrated by sleep. Hill (1953) advocated barbiturate-induced sleep together with basal (sphenoidal) electrodes in all patients with suspected temporal lobe epilepsy. Activation can be achieved equally well with seconal or pentothal (Aungle, Mitchell and Pampiglione, 1954).

The EEG. in Syncope

When fainting is due to a fall in blood pressure (vasodepressor syncope or orthostatic hypotension), or to cardiac asystole, as occurs in the hypersensitive carotid sinus reflex, slow waves of high voltage develop in the EEG. concurrently with the loss of consciousness. When the change of consciousness is very slight and of brief duration, the EEG. changes may be similarly slight, (Engel, 1945). Forster, Roseman and Gibbs (1942) could not find EEG. changes in the circulatory type of carotid sinus syncope nor

in the cerebral type in which no changes in blood pressure or pulse rate occur. However, in the cerebral type slow waves appear either on both sides of the head or, if focal neurological signs appear without loss of consciousness, the slow waves appear on the same side as that on which the sinus is stimulated and contralateral to the neurological signs.

The condition known as vasovagal syncope is classed by Schwab (1951) as "mesencephalic seizure". In these attacks there is "sudden tachycardia, sweating, dilation or constriction of the pupil, paroxysmal alterations of blood pressure and other signs of hypothalamic or midbrain discharges". Usually slow bilaterally synchronous slow waves over frontal and temporal regions occur, but the EEG. changes are very variable. Whether such attacks should be regarded as epileptic remains in doubt. Kershman (1949a and 1949b) studied a group of 180 patients with infrequent spells usually associated with special stress of some kind. These spells consisted of sudden dizziness, blurred vision, sudden loss of consciousness and occasionally a convulsion. Patients with a history of more than three convulsions were excluded, and regarded as epileptic. The group, which have resemblances to that described by Gowrs (1907) were described as sufferers from "encephalosyncope" or "larval epilepsy" since about half of them had a continual diffuse dysrhythmia and the remainder showed frank paroxysmal bilaterally synchronous discharges. This group were followed up clinically and by the EEG. over a period of four to six years. Thirteen per cent had developed convulsions more frequently and were at follow-up regarded as epileptic. In the group of those who never suffered a convulsion, 27 per cent had since developed at least one seizure of major type. No distinction could be drawn between those who had originally shown a diffuse dysrhythmia and those who had shown paroxysmal activity, nor between those who had only brief dizzy spells and those who previously had in addition suffered from a convulsion. Kershman and Hunter (1950) consider the total group a homogeneous one and conclude that patients with such episodic disturbances as dizziness etc. and an abnormal EEG. will subsequently have more severe spells and in about one third of cases a convulsion will eventually occur. Further evidence of the cerebral factor in syncopal attacks is provided by Fuglsang-Frederiksen (1952) who showed that the metrazol threshold was low in 68 per cent of 75 patients suffering from syncopal spells whom he examined. From this group were excluded cases of syncope attributable to circulatory failure. Similar results were

found by Gastaut (1950) using the "myoclonic threshold" obtained by the combined photometrazol technique.

The EEG. in Narcolepsy

Except in cases where narcolepsy follows cerebral trauma and occasionally in postencephalitic cases, the EEG. is normal in this condition. During attacks of narcoleptic sleep the EEG. shows essentially normal sleep patterns. Pond (1952) found EEG. and pulse rate changes identical with those in normal sleep and recorded a period of "EEG. sleep-drift" during an attack of sleep paralysis. The photometrazol threshold was normal in three, doubtful in one, and low in three patients. The responses to photic stimulation alone were normal in all cases.

The EEG. in Migraine

Several EEG. studies have been made in patients presenting with a chief symptom of headache, presumably unassociated with a cerebral pathology. Ulett *et al.* (1952) found abnormal EEGs. in 9·7 per cent of males and 20·5 per cent of females in 1000 consecutive cases. A family history of headache and of migraine, epilepsy or psychiatric disorder predisposed to dysrhythmia. In the cases with vomiting, nausea and hemicrania the EEG. was more likely to be abnormal. Dow and Whitty (1947) found a high incidence of dysrhythmia in migraine in contradiction to Gibbs and Gibbs (1941) who found only a slight excess of EEG. abnormalities in these patients. Roger and Roger (1949) observed that in migraine the alpha activity had an unusual forward extension and that slow rhythms are prominent. There is thus no general agreement about the EEG. in this condition. During teichopsia and scotoma, slow waves at 4-5 c./sec. can be recorded from the affected visual areas, a finding compatible with the vasospastic theory of the disorder (Engel *et al.*, 1944).

The EEG. in Psychiatric Disorders

The early work of P. Davis (1941) demonstrated that in the mentally ill population the EEG. was more abnormal than in the normal population and further that the percentage abnormality in any group studied increased with the severity of the social incapacity of the patients comprising it. Very numerous studies have shown that the incidence of EEG. abnormality increases with increasing failure of adaptation to the stresses of life. This is true of control populations when collected from different groups

(Williams, 1941b; Hill and Watterson, 1942; Gallagher, Gibbs and Gibbs, 1942) and applies to children as well as to adults, to normal groups and to abnormal groups. When from any population are excluded the patients with clinical epilepsy and the patients with focal EEGs. of the type indicating a local pathological process, the remainder shows abnormalities which are, for the most part, unspecific in nature and cannot be related to any known brain disease or metabolic disorder. Many of the records in such cases would be normal for younger persons. An attempt at classification of these various types of abnormality or anomaly, often called "unspecific dysrhythmia" has been made (Hill, 1952). Two main groups were recognized. In the first were those patterns of EEG. found in normal children and normally disappearing as age increases. These, when persisting beyond the expected period of life when they should disappear from the record, were termed "maturation defects". In the second group were placed those EEG patterns not found in normal children and not sensitive to age.

Maturation defects. These patterns decline in incidence as age increases in any population studied. There are four subtypes, often occurring together in the same EEG.: (a) An excess of theta rhythm, (b) alpha variant (subharmonic component of the alpha frequency), (c) posterior temporal slow wave focus at 3-5 c./sec., the waves blocking with the alpha rhythm to visual attention, and (d) the rare theta rhythm dominant record in which this rhythm replaces the alpha frequency. Fig. 23 shows the incidence of such EEG patterns in a normal population and in five abnormal populations.

These patterns of EEG. abnormality or anomaly contrast with those not found in normal children—the paroxysmal disturbances in the EEG. These are of three types: (a) Paroxysmal bilateral symmetrical fast and slow activity, (b) Paroxysmal bilateral spikes of low voltage or spike and waves at 4-6 per second, and (c) Spike foci located in a temporal lobe. These three patterns occur occasionally in normal persons and to a slightly greater extent in some abnormal persons. There are grounds for assuming that their appearance in the EEG. is related paradoxically not to the development of the illness but to recovery from it. For this and other reasons (Hill, 1948, 1950, 1952) they have been given the heuristic title of "homeostatic phenomena". Fig. 24 also gives the incidence of such EEG. patterns in various populations. While "maturation defect" type EEG. patterns are commonest in patients with psychopathic personality, those of the "homeostatic" type

are commonest in schizophrenics. The EEGs. of the maturation defect type are as a group sensitive to overbreathing and to

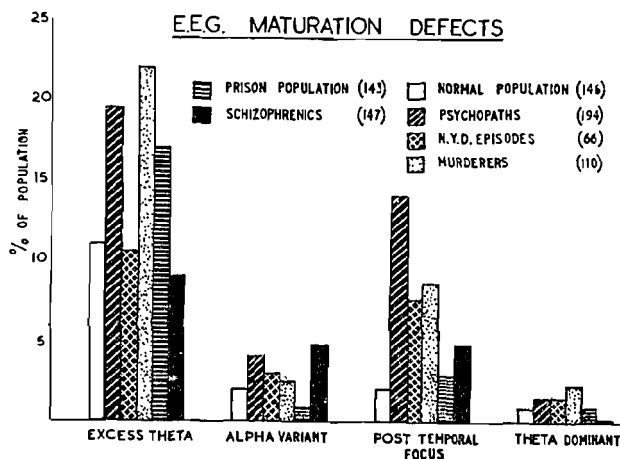


FIG. 23

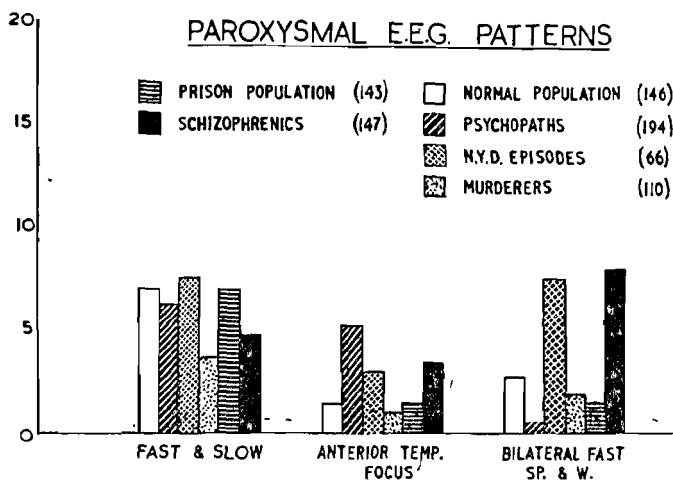


FIG. 24

hypoglycæmia, while those of the homeostatic type are sensitive to photic stimulation, sleep and to hypoglycæmia. Both types of abnormality are found in excess in the EEGs. of epileptics.

Psychological relationships. The EEG. is more frequently abnormal in aggressive, hostile psychopaths than in those of the ineffectual, inadequate type, but attempts to relate aggressiveness as an individual trait with any particular EEG. pattern have failed to show a statistically significant relationship. The most important relationship would appear to be with temporal lobe foci, either slow wave (maturation defects) or spike foci. Of 36 such cases, 28 were markedly aggressive characters. When all EEG. abnormalities are considered together no clear relationship with aggressiveness can be seen either in the psychopathic population (Knott and Gottlieb, 1944) or in the prison population (Stafford Clark *et al.*, 1951). Enuresis after the age of five years, and antisocial behaviour are significantly more common in patients with posterior temporal than anterior temporal foci. The former are, as has been suggested, related to maturation defect. Rey, Pond and Evans (1949) attempted to correlate not the level of intelligence with which no relationship with EEG. characters can be found, but the pattern of different intelligence tests with those characters. They found that the paroxysmal types of EEG. abnormality had verbal test scores significantly lower than their scores on non-verbal tests and that the reverse held for the maturational types of EEG. A larger series of cases investigated by Rey (1954) confirms these findings. It is clear that the difference between paroxysmal and maturational types of EEG. does not relate to any diagnostic categories or to descriptions of personality traits, such as schizophrenic, depressive, psychopathic or hysterical. Thus it is those schizophrenics with paroxysmal EEG. patterns, and only those schizophrenics who as a group show a significant tendency to verbal-nonverbal discrepancy on intelligence tests.

The EEG. in Schizophrenia

Great variability of the EEG. is witnessed in the EEGs. of schizophrenics, but is more frequently abnormal in catatonics than in other groups. The percent-time alpha is very variable and in many cases no alpha rhythm is evident at all. This low voltage fast asynchronous type of record was termed "choppy" by P. Davis (1940) who considered it due to bombardment of the cortex by asynchronous impulses from diencephalic structures—an area which she therefore considered functionally abnormal. For some years the authenticity of the "choppy" record remained in doubt, and the matter can only be settled in the future by electrocortigraphy, but recent work demonstrating abnormal excitability of

these structures in some schizophrenics bring these findings to the fore again. Among catatonics paroxysmal activity, in the form of spikes, slow waves and fast rhythm occurs in 25 per cent of cases (Gibbs, Gibbs and Lennox, 1938b; Jasper, Fitzpatrick and Solomon, 1939). The incidence of such paroxysmal phenomena varies with different stages of the catatonic illness and this variability can be demonstrated and enhanced by hypoglycæmia (Hill, 1948b). A similar variability occurs in the photometrazol threshold, even in those cases in which no paroxysmal phenomena are evident in the resting record. Leiberman and Hoenig (1953) found marked variability with the phases of catatonic stupor, the photometrazol threshold falling to zero as the patient recovered. In other cases the threshold may be zero both in the stuporose and non-stuporose stages of the illness (Corriol and Bert, 1950). It is of great interest that a spontaneous convulsion which may occur or a convulsion induced by photometrazol stimulation or by E.C.T. is the most effective therapeutic method for terminating the stupor. Other evidence showing a decreased excitability of diencephalic autonomic structures in catatonia (Gellhorn, 1943; Hill *et al.*, 1951) and an increasing excitability of these structures with recovery from the illness is relevant. The slow cortical waves which normally result from progressive hypoglycæmia are delayed in appearance in catatonic stupor, as well as the peripheral sympathetic—adrenalin discharges. The EEG. changes as well as cyclical endocrine and metabolic changes (Rowntree and Kay, 1952) which can be demonstrated in many cases may reflect a variation in excitability of diencephalic structures.

These observations apply particularly to the catatonic group of cases and probably only to the cases in which the illness is of recent onset. In the great majority of chronic schizophrenics the EEG. is within normal limits.

Manic Depressive Disorders and Neuroses

No significant abnormalities are seen in these conditions although a proportion of patients suffering from them show anomalous patterns of EEG. of the types already described, particularly maturation defects.

Psychopathic Personality—(see p. 222)

The EEG. findings in this condition are in no way specific or diagnostic, but the records of such patients frequently show an

excess of maturation defects, particularly theta rhythm and posterior temporal slow wave foci. The incidence of abnormalities falls from 70 per cent in the age group 15-20 years to 20 per cent in the group 51-60 years. Paroxysmal phenomena are not seen in excess in this condition. Most patients with abnormal EEGs. show instability of the pattern on voluntary overbreathing, but this is sensitive to the level of blood sugar and to the age of the patient. The posterior temporal slow wave type of defect is more usually associated with the severest personality disorder.

Behaviour Disorder in Children

Since the first study of Jasper, Solomon and Bradley (1938) a large literature has accumulated describing an excess of slow rhythms in the records of children with behaviour disorders. The abnormalities do not correlate well with any specific aspect of growth, such as skeletal maturity, puberty, endocrine factors or intelligence, nor with any specific type of behaviour such as delinquency, thieving or arson, but some correlation with enuresis, hyperkinesis and bad temper has been described. The slow rhythms in abnormal children tend to disappear as age advances. Thus Secunda and Finley (1942) found 74 per cent immature records in four- to nine-year-old children and only 34 per cent of such records in the age group 16 to 18 years.

The factors determining the abnormalities of the EEG. in children as well as in psychopathic adults have occupied many workers, notably Gottlieb, Knott and their associates. (Gottlieb, Ashby and Knott, 1946; Knott, Platt, Ashby and Gottlieb, 1953). The presence of an abnormal family history alone does not increase the probability of an abnormal EEG. in the child, but if to this is added a history of mild cerebral trauma in the child, the EEG. is more likely to be abnormal than when either occurs alone. Epilepsy in the family history is the most important single factor. In their most recent study (1953) these authors provide good evidence for the hereditary factors. In this the EEGs. of the children and both parents were recorded and contrasted with the findings among children brought up by foster parents whose EEGs. were also examined. No meaningful relationship appeared between the EEGs. of foster children and foster parents, but there was a statistically significant trend for patients with slow rhythms to have parents with slow rhythms and the patients with fast rhythms likewise to have parents with fast rhythms in their

EEGs. Thirty per cent of the true parents had abnormal EEGs. with the greatest percentage of abnormality of slow wave types.

The determinants of EEG. pattern are certainly multiple. Heredity is certainly an important one. But trauma at birth or later, anoxia, inflammation and thrombosis can materially affect the maturation processes. What part conditioning processes, learning and environmental factors of a psychological nature play is a matter for future investigation, but these cannot be excluded and possibly constitute the most important factors of all. However this may be, as many have suggested (Williams, 1941b; Hill and Watterson, 1942; Kennard, 1949 and 1953) the patient with minor abnormalities of the EEG. appears to be unduly sensitive to environmental stresses of all kinds, both those which are physiological as well as those which are psychological in nature.

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CHAPTER 13

NEURORADIOLOGY

by

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RECENT years have seen a remarkable increase in the number of specialized radiological investigations performed in centres which deal with neurological and neurosurgical cases. This increase reflects the increasing importance of radiology in neurological diagnosis, particularly in the field of tumour investigation, diagnosis, and localization.

In the following pages the radiological investigations of the nervous system will be considered under the following headings:—

1. PLAIN X-RAY OF SKULL.
2. PNEUMOGRAPHY.
 - (a) ENCEPHALOGRAPHY.
 - (b) VENTRICULOGRAPHY.
3. POSITIVE CONTRAST VENTRICULOGRAPHY.
4. ANGIOGRAPHY.
 - (a) CAROTID ANGIOGRAPHY.
 - (b) VERTEBRAL ANGIOGRAPHY.
 - (c) DURAL SINUS PHLEBOGRAPHY.
5. THE SPINE. MYELOGRAPHY : DISCOGRAPHY.
6. MISCELLANEOUS NEUROLOGICAL LESIONS.

Plain X-rays of Skull-

Radiology of the skull, perhaps more than of any other part of the body demands X-ray films of the best quality taken in a routine manner. For this purpose special apparatus of the type of the Lysholm skull table is, if not absolutely essential, certainly

highly desirable. Such specialized apparatus enables the projections required to be obtained and repeated with a minimum of discomfort to the patient and a satisfactory degree of accuracy and consistency.

For a routine survey of the skull four views are considered to be essential, viz.:—

- (1) Lateral film.
- (2) Postero-anterior film with down-tilt of the tube so as to demonstrate the orbits and orbital fissures clear of the petrous bones.
- (3) "Towne's" view which demonstrates the petrous crests, internal auditory meatus, dorsum sellæ, foramen magnum and occiput.
- (4) A submento-vertical, or basal view.

These four projections and the numerous structures identifiable in them are illustrated in most standard textbooks of radiology.

The skull, however, is such a complex structure that individual cases will often require further special projections to demonstrate a particular pathology, e.g. views of the optic foramina, special views of the mastoids, views of the nasal sinuses, etc.

Plain X-rays of the skull will offer contributory evidence in the diagnosis of a large number of neurological lesions and in a few cases will provide diagnostic evidence not available by any other means.

In cases of intracranial tumour the plain X-rays may provide either (a) general evidence of the presence of a tumour, or (b) local evidence which may identify the anatomical site of the lesion and in some cases even its pathology.

The general evidence of the presence of an intracranial tumour differs somewhat with the age of the patient.

In children the general signs described are:—

- (1) *Suture diastasis.*
- (2) *Sellar changes.*
- (3) *Increased convolutional markings* in the vault.

The former is the most important and the first to be noticed as a rule. The second, in children, only occurs with grossly raised pressure of some standing, and there is always obvious suture diastasis first. The third sign, increased convolutional markings, is one which is given great prominence in many textbooks.

In fact increased convolutional markings are just as common, and often more marked, in children with no evidence of raised pressure as in children with intracranial tumours. An excellent survey of the subject was recently made by Macaulay (1951), who demonstrated this point admirably. Conversely grossly raised intracranial pressure with marked suture diastasis is frequently present in children showing no evidence of "convolutional marking" of the skull vault.

The significance, therefore, of these markings has in the past been grossly exaggerated and the writer feels that they are of little diagnostic importance. As an isolated finding they are insufficient evidence on which to base a diagnosis of raised intracranial pressure.

Turning now to adults, the important general changes suggestive of raised intracranial pressure are, in order of importance:—

- (1) *Sellar changes.* These commence with porosis and thinning of the dorsum sellæ, going on later to actual erosion.
- (2) *Pineal displacement.* In a good quality Towne's film taken on a Lysholm skull table the pineal (which is calcified in about 50 per cent of adults) is found to lie within 3 mms. of the midline. If, on measurement, it lies more than this distance to one side of the midline then that is, almost invariably, positive evidence of the presence of an expanding lesion in one hemisphere. The pineal may also appear displaced in the lateral films but this requires rather more elaborate measurement for assessment.
- (3) *Increased convolutional markings* (so-called). The significance of these has been discussed above. In adults they are of no importance as evidence of raised pressure.

The views on the general X-ray changes of raised intracranial pressure here presented differ somewhat from those which used to be generally accepted, but they reflect what is now believed by most observers especially interested in the subject.

Turning now to local evidence of intracranial tumours, these may be considered under a number of headings.

Intracranial Calcification

This may occur in a variety of *intracranial tumours*. *Gliomas* are the commonest group of intracranial neoplasms, forming about 50

per cent of those seen in routine practice. About 7 per cent of these will show calcification on the plain X-rays and thus localize the lesion. Naturally calcification occurs most commonly in the slow growing tumours such as oligodendrogliomas.

Calcification also occurs in some 10 per cent of *meningiomas*. Many of the latter tumours show a characteristic parasagittal or sphenoidal ridge localization which may suggest the diagnosis.

Craniopharyngiomas also calcify readily. Figures of calcification in these tumours range between 55 and 95 per cent of cases in different series (Bull, 1953). The degree of calcification may vary from a few faint flecks to a dense mass several inches in diameter, but the direct supra-sellar situation and the age of the patient usually suggest the diagnosis.

A number of other less common intracranial tumours may also show calcification (*ependymomas*, *chordomas*, *dermoids*, *pinealomas*, *lipomas* etc.).

Lipoma of the corpus callosum is a rare lesion but has a pathognomonic X-ray picture which enables a diagnosis to be made on the plain films (Sutton, 1949). This consists of two crescentic lines of calcification facing the midline (see Fig. 31f). Diagnosis is important in these cases as the tumour usually involves the anterior cerebral arteries. Attempts at removal may therefore have serious consequences. They are benign and non-progressive lesions and they are best left alone.

Calcification in intracranial tumours may have to be differentiated from calcification due to other lesions. So called "normal" or "physiological" calcification occurs in a variety of intracranial structures. These include the pineal, habenula, and choroid plexuses; the falx, petro-clinoid and inter-clinoid ligaments; the tentorium, the dura, and the Pacchionian bodies. Calcification may also occur in the lens in cases of cataract, when it appears as a ring shadow in the orbit.

Habenular calcification has usually been mistaken for pineal calcification in the past. It is not uncommon and appears as a tiny curved shadow directly beneath the pineal in situation.

The incidence of pineal, ligamentous and other such calcifications shows a steady increase with age, being rare in children and commonplace in the elderly.

The following tables give a list of most of the known causes of pathological intracranial calcification. Certain of these including non-tumour causes will require further consideration.

Pathological Calcification

1. VASCULAR LESIONS.

Arteriosclerosis.
 Aneurysm.
 Angioma.
 Subdural Hæmatoma
 (chronic).
 (Intracerebral hæmatoma).
 (Infarct).

2. INFECTIONS AND INFESTATIONS.

Tuberculoma.
 Tuberculous Meningitis
 (treated).
 Cysticercosis.
 Toxoplasmosis.
 (Hydatid).
 (Schistosomiasis).
 (?? Pyogenic Abscess).
 (?? Pyogenic Meningitis).

3. TUMOURS.

Gliomas (all types).
 Meningioma.
 Osteoma.
 Craniopharyngioma.
 Ependymoma.
 Dermoid and Epidermoid.
 Chordoma.
 Lipoma.
 Pinealoma.
 Hamartoma.
 (Pituitary Tumour).

4. MISCELLANEOUS.

Hypoparathyroidism.
 Pseudo-hypoparathyroidism.
 Basal Ganglia. }
 Dentate Nuclei. }
 Sturge-Weber Syndrome.
 Tuberous Sclerosis.

5. UNKNOWN ETIOLOGY AND NON-SPECIFIC.

The occurrence of calcification in the lesions placed in brackets is either extremely rare or very doubtful.

Toxoplasmosis is a form of infestation which has long been known to affect animals and in recent years has been shown to occur in man. The first recorded human cases were in America some twelve years ago. (Dyke, Wolf, *et al.* 1942). The first case reported in England was that of Jacoby and Saḡorin (1948). Since then a number of cases have been reported in the British Isles, and the writer recently presented five cases all of which were seen within a period of two years (Sutton 1951a). Clinically toxoplasmosis occurs in a latent form in adults, but infestation of the

nervous system of the foetus occurs from "carrier" mothers. This is evidenced in the neonate by a diagnostic tetrad of bilateral chorioretinitis, fits, mental defect, and intracranial calcification. The calcifications, which occur in a high proportion of cases, are usually pathognomonic. They consist of multiple subcortical flecks or linear calcifications, and of similar opacities in the basal ganglia (Fig. 25).

Cysticercosis is an important cause of epilepsy. The work of MacArthur (1933-4) demonstrated the importance of this infestation amongst British troops who had seen service in India. During the late war more British soldiers served in this area than at any other period in our history, and it is likely that a large number of new cases will now be coming to light in this country. The diagnosis of cysticercosis should be suspect in any man who has seen service in India and subsequently develops epilepsy. The radiological features of the infestation in muscle are well known, consisting of multiple oat-shaped calcified cysts. It is now also well known that the intracranial calcified cysts are different in nature. They consist of small multiple discrete rounded nodules from 1-3 mms. in diameter. This is because in the intracerebral cysts only the head or scolex becomes calcified. The incidence of calcification is also much lower in the intracranial lesions than it is in the muscles. Only some 10 per cent of the cases where calcified muscle cysts are demonstrable show intracranial calcifications (Dixon and Hargreaves, 1944). This is an important practical point. It is far more important to X-ray the main muscle masses for evidence of cysticercosis than it is to X-ray the skull.

Tuberculoma is a diagnosis often made on the basis of a focal neurological lesion occurring in a patient with pulmonary tuberculosis, particularly if a calcified intracranial lesion is demonstrated on X-ray. However calcification in intracranial tuberculoma is so rare that the diagnosis can never confidently be made on radiological grounds.

Tuberculoma, once a common intracranial lesion, is becoming relatively rare in this country. It is probable that less than 1 per cent of the true cases of tuberculoma will show calcification (Lorber 1952). Of the few cases of proved tuberculoma seen by the writer none have shown radiologically demonstrable calcification. It is now clear that the diagnosis of tuberculoma on radiological grounds has been made far too readily in the past.

Nevertheless, tuberculosis is likely to be an increasingly common cause of intracranial calcification in future years. The explanation

of this apparent paradox is that large numbers of cases of tuberculous meningitis are now being treated and cured by antibiotics. Lorber has shown that calcification occurs in the basal exudate of an appreciable proportion of these cured cases. Fig. 26 shows an example of such calcification in a child cured of tuberculous meningitis.

Perhaps the most common cause of vascular calcification is *arterio-sclerosis*. Calcification in cerebral arterio-sclerosis is usually situated in the carotid artery as it lies in the cavernous sinus (the so-called carotid syphon). The calcification consists of one or two small irregular flecks, presumably lying in atheromatous plaques. Such calcification is very common and must not be mistaken for calcification in an aneurysm. Demonstrable calcification in the more distal vessels above the sella may occur but is exceedingly rare. The writer, however, has seen two cases with calcification throughout the course of an anterior cerebral artery.

Aneurysms may show calcification in their walls of a characteristic circular or arc-like nature. The vast majority of aneurysms however, show no such calcification and can only be demonstrated radiologically by angiography. Occasionally a large aneurysm will produce local erosion of the upper end of the sphenoidal fissure and of the lateral wall of the optic foramen, an appearance which is almost diagnostic.

Angiomatous malformations are relatively common lesions and in about 14 per cent of cases show some evidence of calcification. This usually consists of a few irregular flecks, of the type associated with atheroma, and occasionally of concomitant ring-like calcifications. The latter lie in aneurysmal dilatations in the malformation. Angiomas are further discussed below under cerebral angiography.

Chronic subdural hæmatoma which has been present for years may also calcify when the lesion appears as flat irregular plaques against the skull vault or around the hæmatoma.

Calcification of the basal ganglia may occur in several conditions. *Hypo-parathyroidism*, usually of idiopathic origin, is probably the commonest cause (Camp, 1947). Similar calcification may also occur in the rarer *pseudo-hypo-parathyroidism* (Medill, 1951), and *toxoplasmosis* can also cause local calcification in the basal ganglia. (Camp, 1947). Occasionally no etiological factor can be demonstrated for such symmetrical calcification in the basal ganglia, as in the small group of familial cases reported by Foley (1951).

Epiloia, or tuberous sclerosis, is associated with intracranial

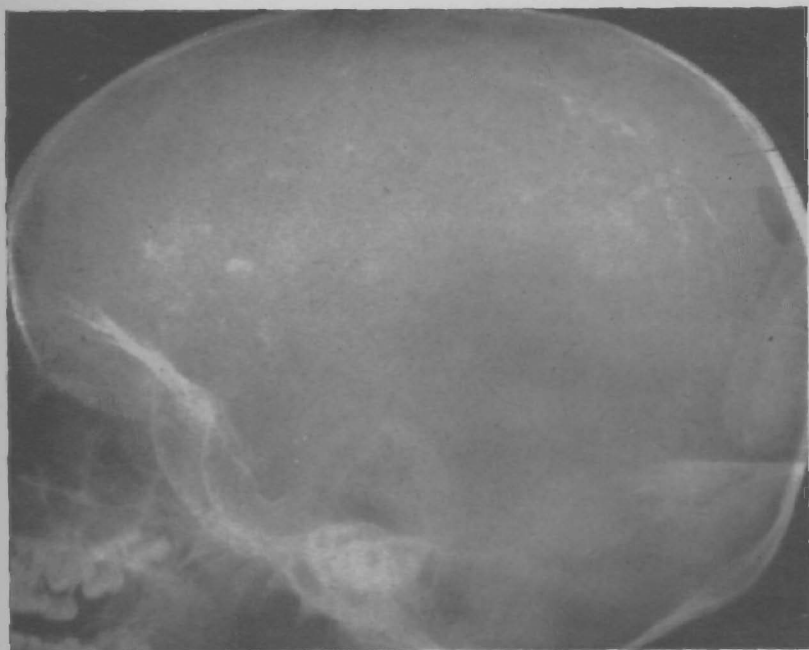


FIG. 25. Toxoplasmosis. Note the pathognomonic multiple flake-like subcortical calcifications.



FIG. 26. Calcification in basal exudate above and behind the sella in a case of tuberculous meningitis cured by streptomycin.

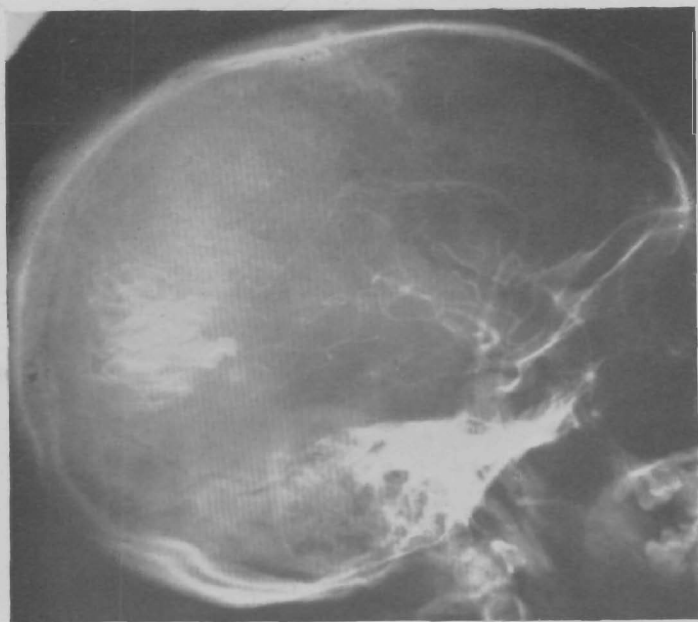


FIG. 27. Cerebral angiogram in a case of Sturge-Weber syndrome. Calcification is in an area of atrophic brain cortex. There is no evidence of increased vascularity.

calcification in a high proportion of cases. The calcification tends to develop in the cerebral nodules and to become more marked after puberty. Classical cases show several discrete subcortical and paraventricular calcifications of low density and about 3–5 mms. in diameter. Large atypical and single calcifications of irregular shape may, however, be seen (Sutton, 1951b). Several other important radiological changes may occur in cases of epiloia. Thus the skull vault may show patchy areas of increased density, and pneumography may reveal characteristic intraventricular nodules, which has been likened to “candle guttering”.

Sturge-Weber syndrome (trigeminal angiomatosis) is well known to be associated with a very typical intracranial calcification, the so-called “tram-line calcification”. In many textbooks photographs of these calcified lesions are reproduced with a legend describing them as “calcification in an intracranial angioma in Sturge-Weber disease”. However, as long ago as 1936 Krabbe showed that the calcification was not in an angioma but in the surface of atrophic brain tissue which was overlain by thickened meninges. There is in fact no evidence of an intracranial angioma and angiography in these cases provides negative results (Fig. 27). The calcification in these cases is nearly always unilateral, though occasionally cases with bilateral calcification are seen. It usually commences in the occipital region and spreads forward to a varying degree.

Local Erosion; Sellar and Foraminal Expansions

Evidence of the presence of intracranial tumour may also be provided by local erosions of the skull wall, or by erosion or expansion of the sella, or of various foramina.

Thus *acoustic neuroma* will locally expand the internal auditory meatus and produce a funnel shaped deformity readily recognizable on plain X-rays. This is usually detectable on the routine “Towne’s” projection (Fig. 35d), though special views may be necessary for confirmation.

Glioma of the optic nerve is a relatively rare lesion but will produce a very characteristic expansion of the optic foramen on the affected side which is easily demonstrable by X-rays. Local erosion of the sphenoidal bones around the upper end of the orbital fissure may be seen with large *retro-orbital aneurysms*. Such aneurysms may also erode the lateral margin of the optic foramen.

A similar deformity may be produced by a *meningioma* although these tumours more commonly give rise to hyperostosis in this

region. Local erosion of the skull may also occur in any of the other typical meningioma sites, although this is less common than is hyperostosis or a mixed hyperostosis and erosion. Unilateral enlargement of the foramen spinosum is another important sign which often occurs with meningiomas owing to the enlargement of the meningeal vessels on the affected side.

Skull defects may occur from *secondary deposits*. They may also occur in lipoidoses and reticulososes, in inflammatory lesions, and in a number of generalized diseases. The differential diagnoses of these lesions is too large a subject to discuss in this chapter.

Pituitary adenomas may be of three varieties, (1) chromophobe, (2) acidophil, and (3) basophil. Sellar changes, consisting of generalized enlargement or "ballooning", are seen with diminishing frequency in the three groups. Thus with chromophobe adenomas the sella is often grossly enlarged by the time the case presents clinically. With acidophil tumours sellar enlargement is frequent, but may be absent or negligible. In cases of basophil adenoma the sella is never enlarged as the lesions are microscopic. On radiological ground the differential diagnosis of a "ballooned" sella therefore lies between chromophobe and acidophil adenoma. The differentiation is usually as clear on the X-rays as it is clinically. The chromophobe adenoma is associated with a normal skull apart from the sellar lesion; the acidophil adenoma on the other hand lies in a skull showing the characteristic changes of acromegaly, i.e., prognathous jaw, enlarged sinuses, and thickened vault.

Hyperostosis

From the neurological point of view the most important type of hyperostosis is that associated with local bony reaction due to the presence of a *meningioma*. Such a bony reaction should always raise suspicion when it occurs in the characteristic meningioma sites, i.e. parasagittally; along the sphenoidal ridge; in the olfactory groove region, or elsewhere in the base of the skull.

The benign hyperostosis of *hyperostosis frontalis interna* is readily recognized for it is typically bilateral, spares the midline, and affects only the inner table of the skull. It occurs with a very high degree of frequency in menopausal females. The incidence in fact is so high that the appearance may be regarded as within normal limits in any female above the age of 40. Attempts to associate the lesion with clinical findings as in the Morgagni and Stewart-Morel syndromes usually ignore this fact. It is probable

that the association in such "syndromes" is purely coincidental (Pedersen, 1947).

Hyperostosis, like bone erosion, may occur in a large number of non-neurological disorders ranging from fibrous dysplasia to chronic bone infections, and including such diverse lesions as secondary deposits and Paget's disease. As with the subject of skull defects it is not possible within the limits of this chapter to discuss in detail the differential diagnosis of these lesions.

Increased Vascular Markings

There is a large variation in the degree to which the normal skull shows vascular impressions, either meningeal or diplœtic. Grossly increased meningeal markings however, if generalized and symmetrical, are usually associated with the presence of an intracranial angioma. Locally increased meningeal and diplœtic markings may be associated either with an angioma or with a meningioma. In such cases the foramen spinosum is enlarged on the affected side.

It will be seen from the above discussion that plain X-ray of the skull can of itself provide valuable information in a large variety of intracranial lesions and particularly in the investigation of intracranial tumours. In many cases, however, further information will be provided, even in cases where plain X-rays are normal or equivocal, by the use of more elaborate X-ray diagnostic methods and these will now be discussed.

Pneumography

Visualization of the ventricular system using air or other gases as contrast medium dates back to the end of the first World War. Dandy (1918) was the first to conceive the idea of deliberately injecting air into the ventricles. Previously accidental air visualization of the ventricles had been reported by Lockett (1913) in a patient who had suffered a severe head injury followed by traumatic ærocele. Dandy demonstrated that air could be introduced by a cannula passed through the brain after a burr hole had first been made (*ventriculography*). A year later the same neurosurgeon showed that air visualization of the ventricles could be obtained by means of air injected into the subarachnoid space at lumbar puncture (Dandy, 1919). The latter procedure is known as *encephalography*. Both methods of pneumography have been widely practised since their introduction.

Technique of Ventriculography

Ventriculography is performed by the neurosurgeon in the operating theatre. Posterior parietal burr holes are made and the ventricles injected by means of a cannula passed directly through brain tissue. The patient is then brought to the X-ray department where films are taken appropriate to the suspected lesion and the findings on the preliminary X-rays.

Technique of Encephalography

Encephalography should be performed in the radiological department. With adults the procedure can usually be carried out under local anaesthesia. The patient sits facing the skull table with his orbito-meatal line inclined at an angle of about $15-20^{\circ}$ downwards from the horizontal (Fig. 28). The importance of correct positioning of the patient cannot be over emphasized and is well illustrated by Robertson (1941, 1946). The air may be injected either by the lumbar or the cisternal route. Some workers have strong predilections for one route against the other, but this is largely a matter of personal preference and experience. Equally good results can be obtained by either method, but for technical reasons the lumbar method is to be preferred, as it simplifies radiography.

An important point is that it is unwise to perform lumbar encephalography within about ten days of a previous lumbar puncture. Lumbar puncture always tends to open up the potential subdural space because of fluid seeping back at the puncture site. This may result in the space becoming fluid filled, and then at the later encephalographic lumbar puncture the distended subdural space may be entered instead of the subarachnoid space. Fluid will drip back, and the operator may be deceived into injecting his air subdurally with resultant failure to obtain diagnostic films.

Once the subarachnoid space has been punctured as evidenced by a backflow of cerebrospinal fluid, the needle stilette is inserted and no fluid is allowed to escape until air is first injected. The gas is injected at a rate of 5-10 ml. at a time. The injection is made very slowly taking several minutes for each small quantity of air. For each 5 ml. of air injected a corresponding 5 ml. of fluid are allowed slowly to drip back. Thus at no time is there much change in the total volume of fluid and air in the subarachnoid space. The important point is that for each small injection of air a compensatory amount of fluid is withdrawn, and the air must be put in first (Lindgren, 1949).



FIG. 28. Patient in position for lumbar encephalogram. For clarity the tube of the Lysholm table has been moved from the lateral to the posterior position with relation to the head.

At the end of the first injection of 5–10 ml. of air a lateral film is taken with a horizontal beam of X-rays. This film should show the aqueduct and 4th ventricle well filled with air and is the best means of demonstrating these structures in lateral view. A further film, this time in the postero-anterior plane, is taken after the injection of the next small quantity of air. This demonstrates the aqueduct and 4th ventricle in the frontal plane and whether or not they are lying normally in the midline.

No further air is injected until these films have been inspected. This is necessary, firstly as a check on whether or not the ventricular system is being filled, and secondly because some air will pass into the lateral ventricles and enable their general size to be assessed. On this assessment depends the total amount of air injected. If the ventricular system appears normal in size, up to 35 ml. of air are injected altogether. This amount will give very adequate filling for diagnostic purposes. In the case of unobstructed and grossly dilated ventricles however, as in some atrophies, double this quantity of air or more may be necessary to achieve equivalent filling. On the other hand, if no air has entered the ventricular system, or if a gross displacement of the aqueduct or 4th ventricle is present, or some other abnormality is seen suggesting an intracranial tumour, the quantity of air injected is accordingly diminished. In tumour cases (which are further discussed below) it is not usually necessary to inject more than 15 ml. of air. With a careful technique this is adequate for diagnostic purposes.

In many cases it may also be necessary to demonstrate the basal cisterns and cortical air channels. The former may be filled to some degree on the original two films taken whilst the air is being injected. However, to fill both these and the cortical channels well it is usually necessary to inject an extra 5–10 ml. of air with the patient's chin elevated so that the orbito-meatal line is angled slightly upwards. Once the final injections of air have been made and the needle has been removed, the patient is placed supine, and routine or other films are taken according to the particular problems presented.

Complications

Both ventriculography and encephalography are procedures which have been associated with important complications.

The replacement of cerebrospinal fluid by air may result in a considerable disturbance of the intracranial pressures. In patients

with raised intracranial pressure and incipient tentorial or medullary pressure cones such interference could have the gravest consequences. There is no doubt that in the early days of these procedures, many such patients died because of pneumographic investigation. Encephalography was undoubtedly the more dangerous procedure in this respect; but ventriculography also had a serious mortality risk, mainly because it was reserved for the more seriously ill patients. As a result ventriculography in tumour cases was generally undertaken only as a pre-operative measure, and encephalography not at all. Should the ventriculogram considerably upset the patient and tend to produce coning, operation could be undertaken rapidly and a decompression performed. In these circumstances the risks of ventriculography even in seriously ill patients with gross papilloedema and incipient coning, have been considerably diminished.

There are several other complications of ventriculography. The writer has seen both subdural hæmatoma and a large intracerebral hæmatoma following the procedure. Recently Falk (1951) has demonstrated that an appreciable proportion of patients who have undergone ventriculography develop calcifications in the needle track some years later. It is thought that these are due to calcification in small hæmatomas. Fatal air embolism has also been recorded following ventriculography (Heppner, 1952).

Nevertheless, in most cases of tumour the value of the diagnostic evidence provided by ventriculography far outweighs the risks associated with the procedure. Minor complications which occur at pneumography, such as headache, nausea and vomiting, merely emphasize that the investigation should not be performed too lightly. The latter are usually far more prominent at encephalography than at ventriculography.

Encephalography, as has already been made clear, used to be an extremely dangerous procedure to undertake in patients with raised intracranial pressure. Recent Swedish work, however, has shown that the dangers are due not so much to an inherent defect of the method but to features of the technique which can be guarded against. Thus if fluid is taken out of the spinal subarachnoid space the pressure in it will be lowered and there will be an even greater tendency than already exists for grossly raised intracranial pressure to cause "coning". If however, as described above, only a small quantity of fluid is drawn off (and that only after preliminary injection of an equivalent quantity of air), the pressure in the spinal subarachnoid space need never be signi-

ificantly altered. With this fact in mind it is possible to perform encephalography in tumour cases with no more risk to the patient than occurs at ventriculography. This technique of "controlled encephalography" using small quantities of air has now been practised in Stockholm for several years and in a large series of tumour cases. The mortality and morbidity compare most favourably with that of ventriculography (Lindgren, 1949, 1950a, Falk 1953).

Indications

To summarize some points from the above discussion. It has been usual in the past to reserve ventriculography for the investigation of patients with intracranial tumours and suspected neoplasms. Encephalography on the whole has been practised for the investigation of intracerebral lesions not associated with raised intracranial pressure. These included epilepsy not due to tumour, cerebral atrophies, congenital brain lesions, post-traumatic conditions, and such other neurological and neurosurgical lesions as were likely to show abnormalities of the ventricular system but were not associated with raised intracranial pressure. In recent years however, with improvements in encephalographic technique the accepted indications for or against ventriculography or encephalography have undergone some change, and encephalography is now encroaching more and more upon the field of tumour investigation formerly reserved for ventriculography.

Radiographic Technique

Details of radiographic technique need not be considered here, but generally speaking the best results are only obtained where the whole investigation is carefully controlled by the radiologist. In these days no surgeon would consider as adequate a barium meal examination where the patient drank the barium and a few standard films were taken by a radiographer. He must rely on the careful screen examination of the radiologist, which, because of his special experience, enables him to detect and film lesions which would otherwise remain undemonstrable. Similarly a pneumographic investigation carefully controlled and supervised by a radiologist with special experience in this type of work will product far more significant results than will a few standard films taken after haphazard air injection of the ventricles.

Pneumographic Appearances in Intracranial Tumours

The diagnosis and localization of intracranial tumours by pneumography is too large a subject to be dealt with in detail in a work of this nature. It is proposed in this chapter merely to outline general principles of tumour localization and to discuss a few of the more interesting lesions specially studied in recent years.

The interpretation of pneumograms requires familiarity with the appearances seen in normal cases. These are well described in the standard textbooks of radiology. Further detailed studies of pneumography will be found in the classical works of Lysholm (1935 and 1937), Twining (1939), Robertson (1941, 1946) and Lindgren (1949).

Intracranial tumours are naturally classified as either supratentorial or infratentorial.

Supratentorial tumours may be further classified as either lateral or midline. A careful study of the pneumograms will usually enable an accurate localization of the lesion to be made.

With laterally placed tumours in the hemispheres the cardinal sign is a displacement of the septum pellucidum and 3rd ventricle away from the side of the lesion. The height of the tumour in the hemisphere, i.e. from high parasagittal to basal, can be roughly assessed at a preliminary survey by the angulation of the septum and 3rd ventricle, and by other features. Fig. 29 illustrates this point.

The localization in the antero-posterior plane is indicated by the deformity of the individual parts of the lateral ventricle such as the frontal horn, body, or temporal horn (Fig. 30). Lindgren has shown that very precise localization of temporal tumours can be made if the temporal horn is specially filled and studied in such cases (Lindgren, 1948).

As regards midline tumours, these include gliomas of the corpus callosum, lipoma of the corpus callosum, glioma of the septum pellucidum, 3rd ventricle and para-3rd ventricle tumours, suprasellar tumours and tumours of the olfactory groove. All the above have characteristic pneumographic appearances a number of which are illustrated in the accompanying diagrams (Figs. 31a to 31g).

Suprasellar tumours include craniopharyngiomas, extensions from pituitary adenomas, meningioma of the tuberculum sellæ, chiasmatic glioma, and aneurysms. If aneurysm or meningioma are suspected angiography as well as pneumography will be necessary for diagnosis.

Tumours in and around the 3rd ventricle form an interesting group and were the subject of a monograph by Dandy (1931).

The writer in association with Dr. J. W. D. Bull has been especially interested in these lesions. The conclusion was reached that there was in fact only one significant tumour of the 3rd ventricle, i.e. the so-called "colloid cyst" or "paraphysial cyst" (Bull and Sutton, 1949). Nearly all the other tumours described as 3rd ventricle tumours are actually tumours of structures around the 3rd ventricle and encroaching on it.

Paraphysial cysts are of particular radiological interest. In our group of 24 cases the diagnosis was rarely even suggested on clinical grounds, whilst ventriculography prompted an accurate pre-operative diagnosis in all but one case. The pneumographic appearances are in fact pathognomonic. (See Figs. 32 and 33.)

Infra-tentorial tumours have received particular attention in recent years. Filling of the aqueduct and 4th ventricle at ventriculography demands a careful technique and controlled manipulation of the air by the radiologist in the X-ray department. Alternatively these structures and the basal cisterns may be well shown by encephalography performed as described above. With such techniques the aqueduct and 4th ventricle will be adequately demonstrated in the majority of cases. The various appearances with the different posterior fossa tumours are illustrated in the accompanying diagrams (Fig. 34). It will be seen that the precision of radiological localization in cases of posterior fossa tumour should reach a very high degree. It is, therefore, remarkable that in many centres both clinicians and radiologists should have rested content until recent years with a radiological diagnosis which went no further than "symmetrical hydrocephalus with dilated 3rd ventricle—probably posterior fossa tumour". Today it is only in a very exceptional case that a tumour is operated on in the more enlightened centres unless precise radiological localization has first been achieved. Such localization owes much to the studies of Lysholm (1937, 1946) and of Twining (1939).

The writer has been particularly interested in improving the diagnosis and differential diagnosis of pontine tumours. Details concerning these lesions will be found in separate publications (Sutton, 1950, 1953).

Relationships which have been found particularly useful in the assessment of posterior fossa tumours are:—

1. Twining's kink (Fig. 34b). This is a sharp posterior angulation of the aqueduct resulting from posteriorly placed tumours pressing the 4th ventricle forwards and to which attention was first drawn by Twining (1939).

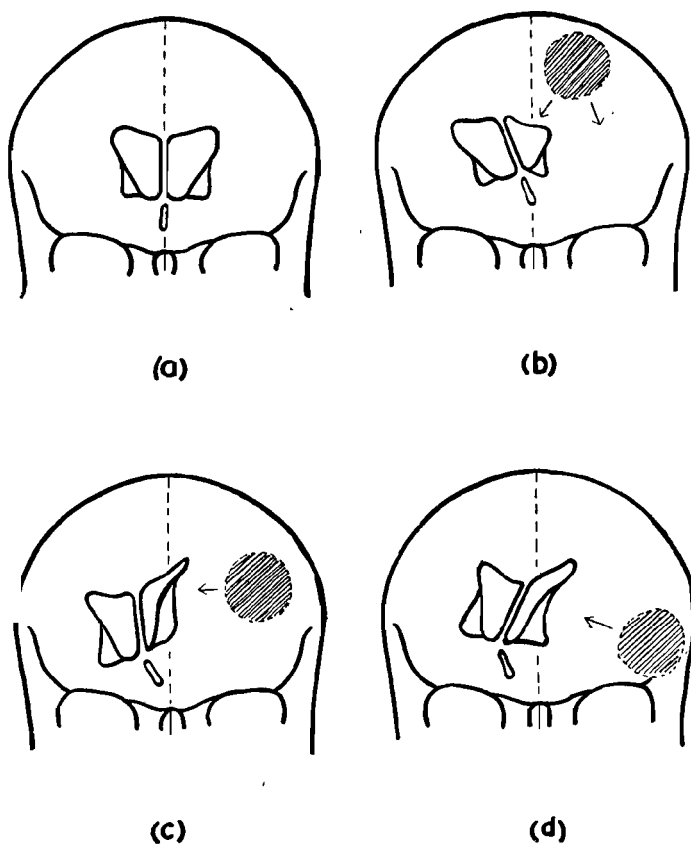


FIG. 29. Supratentorial tumours. Diagram to illustrate tumour localization in the frontal plane.

(a) Normal.

(b) High parasagittal tumour.

- (Note: i) the septum and 3rd ventricle lie in the same plane,
 ii) the supero-lateral angle of the lateral ventricle is blunted on the side of the tumour.

(c) Laterally placed tumour.

- (Note: i) Displaced septum and 3rd ventricle are slightly angled to each other.
 ii) Supero-lateral angle of the adjacent ventricle is slightly narrowed.

(d) Low lying (temporal) tumour.

- (Note: i) Septum and 3rd ventricle are sharply angled.
 ii) Supero-lateral angle of lateral ventricle is squeezed and narrowed.

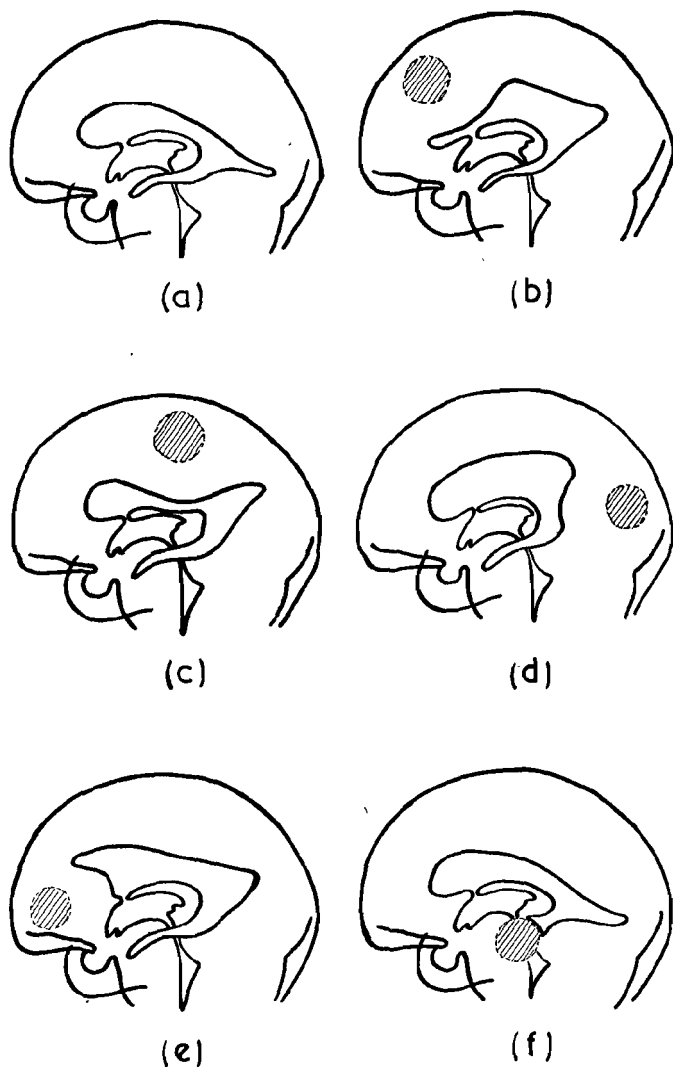


FIG. 30. Supratentorial tumours; tumour localization in the lateral view.

- | | |
|-----------------------------------|------------------------|
| (a) Normal appearances. | (d) Occipital tumour. |
| (b) High frontal tumour. | (e) Subfrontal tumour. |
| (c) Parasagittal parietal tumour. | (f) Temporal tumour. |

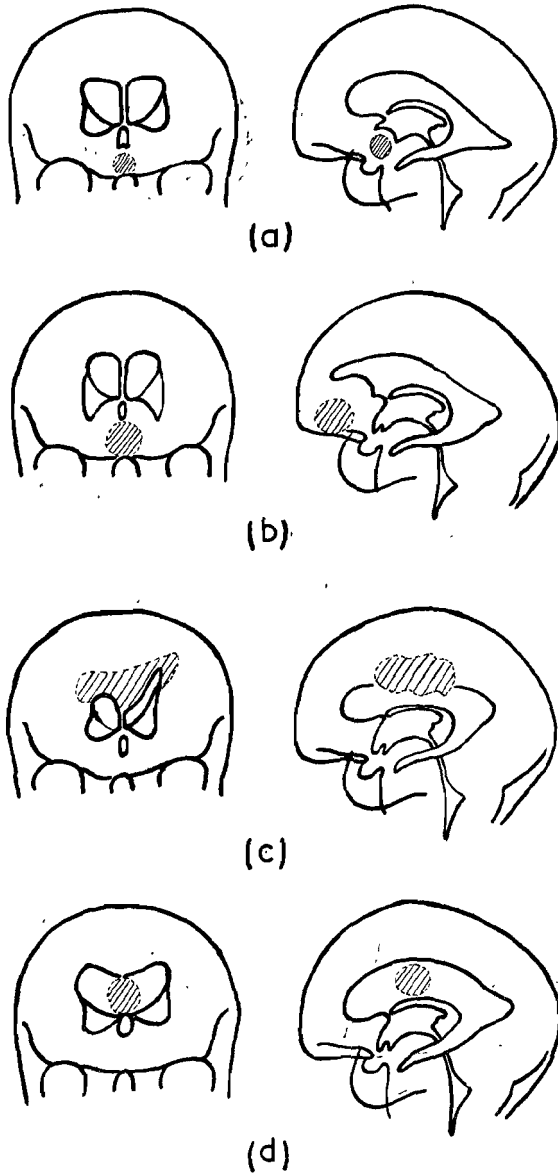


FIG. 31. (For explanation see opposite page.)

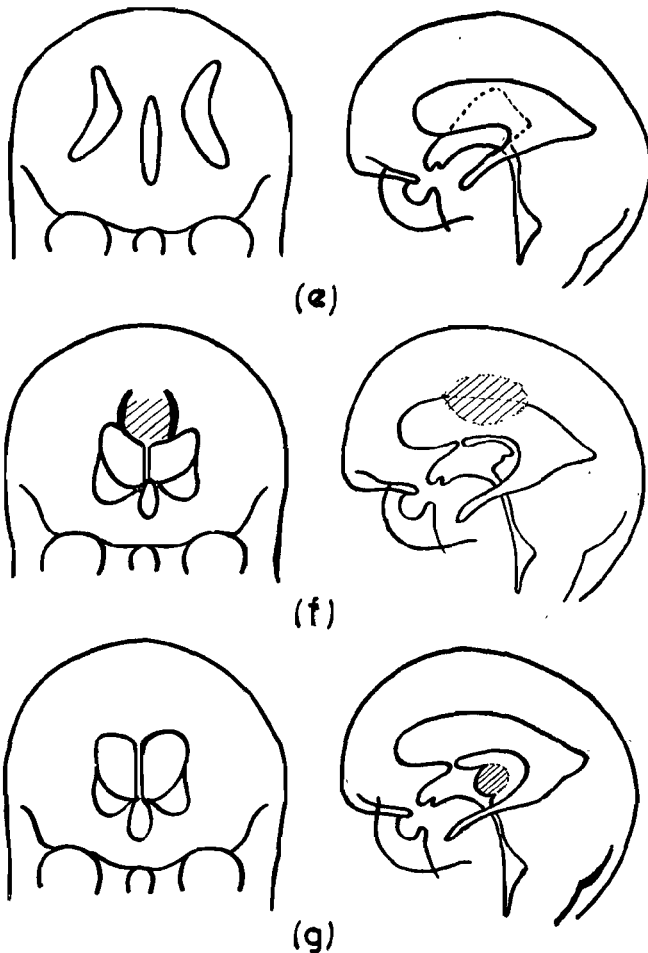


FIG. 31. Midline supratentorial tumours and other conditions.

- (a) Suprasellar tumour.
- (b) Subfrontal tumour.
- (c) Tumour of the corpus callosum.
- (d) Tumour of septum pellucidum (cysts of the septum are biconvex rather than rounded). The above two conditions should be differentiated from e and f.
- (e) Agenesis of the corpus callosum.
- (f) Lipoma of the corpus callosum. (Note pathognomonic crescentic calcifications facing the midline in antero-posterior view.)
- (g) Pineal tumour or cyst.

2. Twining's line—a line joining the tuberculum sellæ to the internal occipital protuberance as seen in a lateral film of the skull. This mid point of this line normally lies in the 4th ventricle (Fig. 34a). The point lies anterior to the 4th ventricle in the case of pontine and other anteriorly placed tumours even when the displacement is minimal (Fig. 34f).
3. Lysholm's line—a line from the clivus through the aqueduct to the skull vault. The aqueduct normally lies below the junction of the first and middle thirds (Fig. 34a).

Although ventriculography will permit adequate visualization of the aqueduct and 4th ventricle in the majority of cases it occasionally happens that, despite an adequate technique, good filling of the posterior fossa structures cannot be obtained. This usually occurs when the 3rd ventricle is small and slit-like. In such cases two methods are available. As already indicated, encephalography (using a small quantity of air only) may solve the problem. (Incidentally a successful "encephalogram minor" will enable the basal cisterns to be seen and may even outline an extracerebral tumour.) Alternatively positive contrast ventriculography will enable the answer to be obtained.

Positive Contrast Ventriculography

Attempts to visualize the ventricular system by means of positive contrast instead of with the negative shadows of pneumography date back many years. The first medium suggested was Lipoidol. This has been claimed to give satisfactory results by several writers but has been denounced as a possible cause of ependymitis and aqueduct stenosis by others. Apart from a few workers it has been generally given up. In 1936 Twining and Rowbotham suggested the use of Thorotrast. This medium also enjoyed only a short and temporary vogue, owing to the alleged danger of radio-activity, and to experimental proof of ependymitis resulting from its use in dogs. In recent years Bull (1950) has suggested the use of Ethyl Iodophenylundecilate (proprietary preparations are Myodil, Ethiodan, and Pantopaque). This has now been used on well over 100 cases at the National Hospitals for Nervous Diseases without any dangerous results. The technique is essentially the same as that elaborated for use with Lipoidol and described by Lysholm (1937). It requires careful radiological screening of the patient in order to manipulate the contrast into the correct positions. The injection is made into the upper lateral ventricle with the patient's head hanging down sideways, in such a



FIG. 32 (a).



FIG. 32 (b). (*For explanation of these figures see overleaf.*)



FIG. 32 (c).

FIG. 32. Colloid cyst of the 3rd ventricle as shown in three projections (see also Fig. 33).

- (a) Antero-posterior. Note the rounded cyst shadow superimposed on the lower end of the septum pellucidum.
- (b) Towne's. The cyst shadow appears ovoid and is well seen.
- (c) Lateral. The rounded shadow lies directly behind and partially blocking the foramen of Monro.

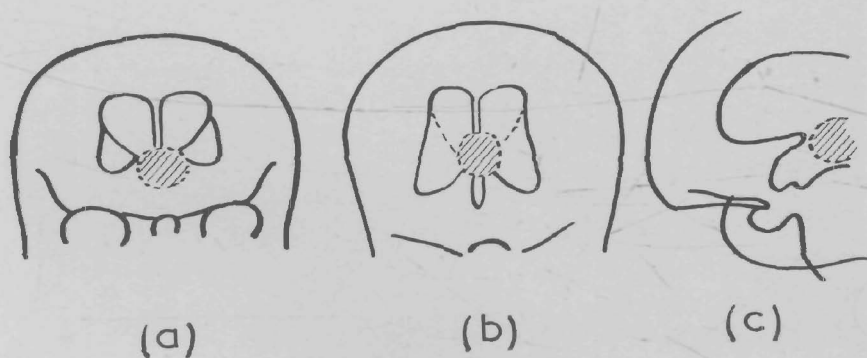


FIG. 33. Diagram to illustrate Fig. 32.

way that the contrast falls into the anterior horn. The head is then manipulated under screen control in order to fill the posterior fossa structures. The type of diagnostic result obtainable is shown in the accompanying illustrations (Fig. 35). It is most important to ensure that the injection is being made into the ventricle. The writer has encountered two cases where extraventricular injections have been made. In both cases, however, no apparent sequelæ were observed. Occasionally difficulty is encountered in making the contrast pass through the foramen of Monro, but this can usually be overcome by persistence and patience.

Cerebral Angiography

Carotid Angiography

The widespread adoption in recent years of routine percutaneous cerebral angiography is undoubtedly the most important advance in neuroradiology since the introduction of pneumography 35 years ago. Intracranial diagnosis by angiography, however, dates back over a quarter of a century and the value of the method was clearly established by Moniz who published monographs on the subject in 1931 and 1933. His enthusiastic advocacy of angiography went largely unheeded for two reasons. Firstly the contrast media then available, sodium iodide, and later thorotrast, were suspect. Secondly, Moniz's method involved exposure of the artery by open operation, and few cared to subject the patient to an operation for what was merely a diagnostic procedure. The picture has been changed in recent years, however, by the introduction of a relatively innocuous contrast medium in Diodone, and by the re-development of the percutaneous technique of arterial puncture. Thus there has been made possible, with very little risk, or even inconvenience, to the patient, a hitherto unobtainable precision and accuracy in the diagnosis of a large number of intracranial lesions. Formerly such precision could only be obtained by operation or autopsy.

The technique of percutaneous angiography has been adequately described by Lindgren (1947). A certain amount of experience is necessary before successful injections can be obtained routinely but the method is now well established in most neurological and neurosurgical centres.

A number of complications have been described. In the writer's opinion many of these were due to inexperience of the operators or to faulty technique. In a series of some 2,000 cases injected in

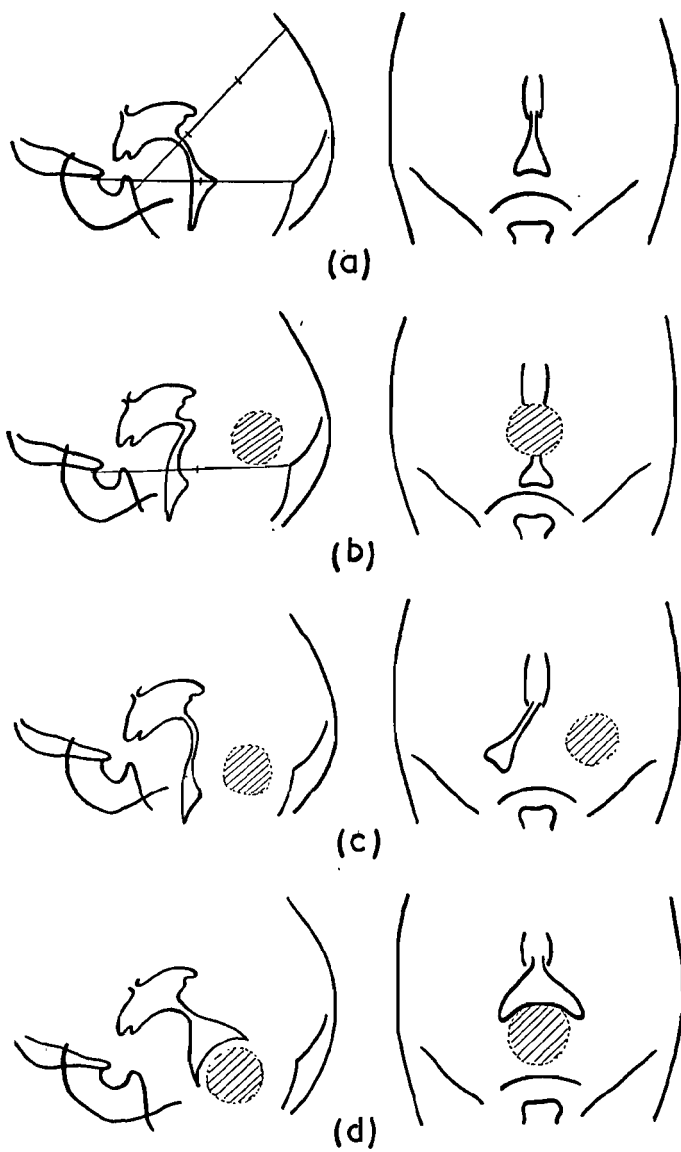


FIG. 34. (For explanation see opposite page.)

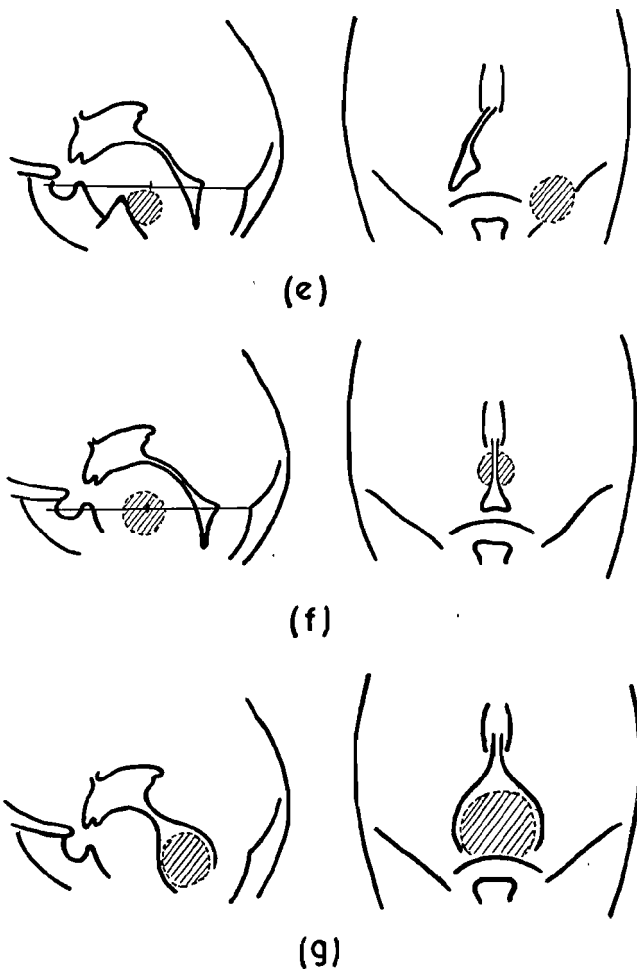


FIG. 34. Tumours of the posterior fossa.

- (a) Normal relationships with Twining's line, and Lysholm's line. (See text.)
- (b) Vermis tumour. (Note "Twining's kink".)
- (c) Cerebellar hemisphere tumour.
- (d) Midline intrafastigial tumour.
- (e) Cerebello-pontine angle tumour.
- (f) Pontine tumour.
- (g) Fourth ventricle tumour.

the last six years serious complications have been negligible. Considering that a large proportion of these cases had intracranial tumours and many were in a serious condition, (some even in coma at the time of examination), it is not surprising that there has been an occasional death within 24 hours of the angiogram. In the four autopsies of such cases personally investigated large tumours with tentorial pressure cones were present in all. It is certain that in such cases the only other investigation possible to localize the lesion, i.e. ventriculography, would have been associated with a much higher percentage of deaths and morbidity.

Another reported complication of cerebral angiography is hemiparesis. Most of the recorded cases have been transient in nature and there has been complete recovery within a few hours or days. There are, however, on record a few cases where permanent hemiplegia has resulted. It is the writer's opinion that such complications should be extremely rare provided the technique is satisfactory and injections are made with Diodone of low concentration. Ten mls. of 35 per cent Diodone is adequate for lateral films and ten mls. of 42 per cent Diodone for antero-posterior films. Concentrations of the drug higher than these should only be used in exceptional circumstances; for example in cases of large angiomatous malformation where adequate visualization would be obtainable only with the stronger solutions. Many of the more serious reported complications of angiography were due to the mistake of using the drug in too high concentration and in too large quantity. The experimental work of Broman and Olsson (1948) has shown that high concentrations may affect the so-called "blood-brain barrier".

The incidence of minor complications such as hæmatoma formation is inversely proportional to the experience of the operator.

The importance now attached to cerebral angiography can be appreciated from the comparative figures of the number of these angiograms done in the last few years at the National Hospitals for Nervous Diseases (National Hospital, Queen Square, and Maida Vale Hospital for Nervous Diseases). Before 1946 the investigation, which was always done by open operation, was only rarely performed. Since that year the figures for the two hospitals have been:—

1946— 60 cerebral arteriograms
1947—180 cerebral arteriograms
1952—650 cerebral arteriograms

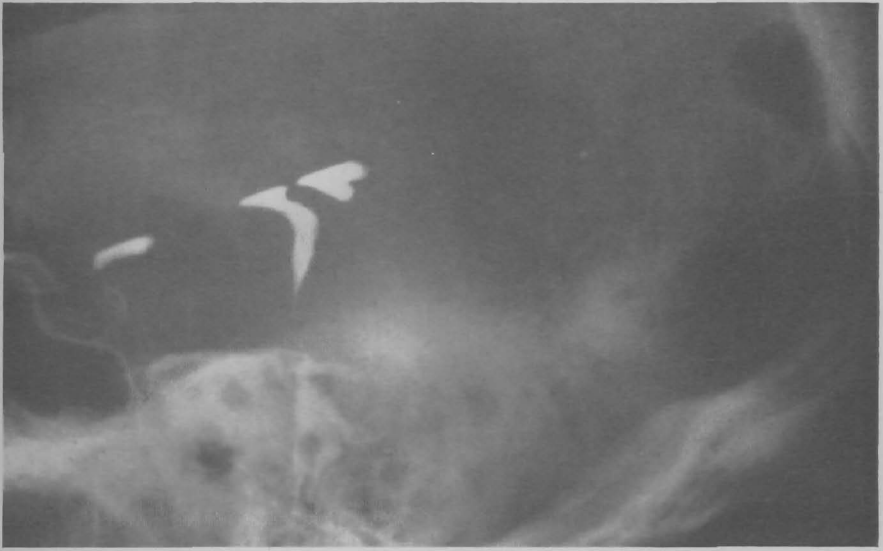


FIG. 35 (a).

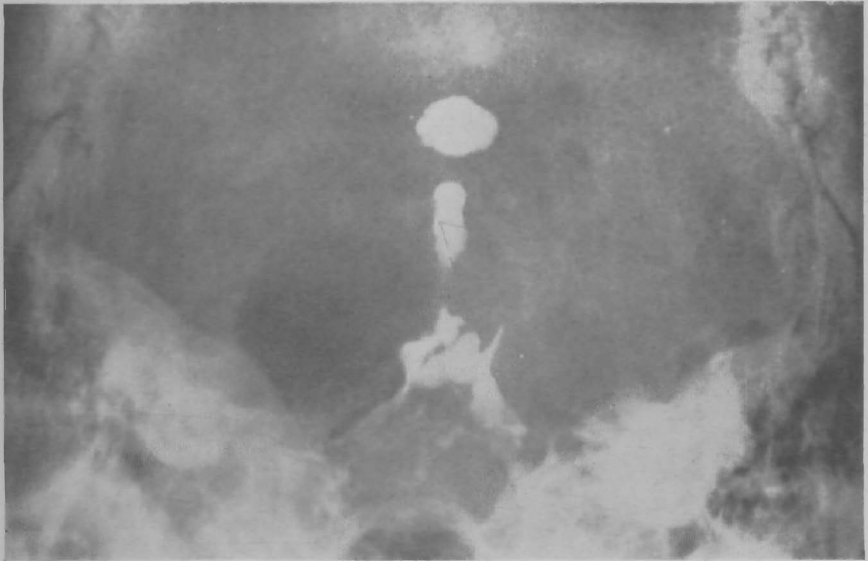


FIG. 35 (b).

FIG. 35. Myodil ventriculograms.

(a and b) Vermis tumour. Compare Fig. 34b.
(c and d) See overpage

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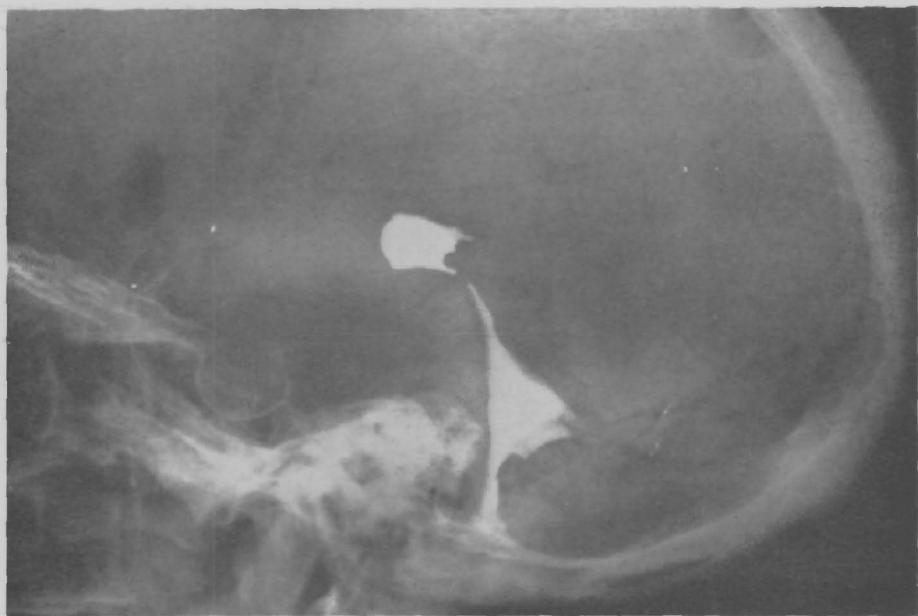


FIG. 35 (c).

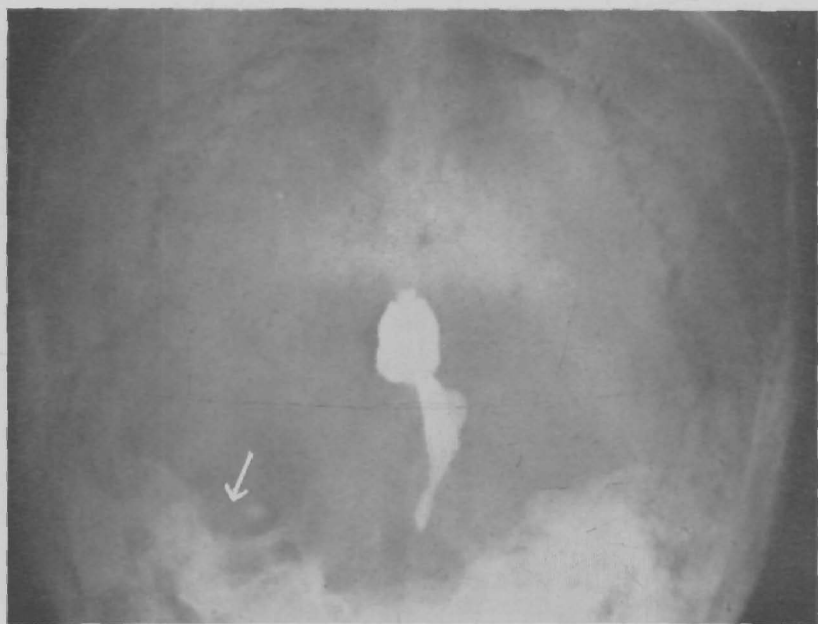


FIG. 35 (d).

(c and d) Acoustic tumour. Compare Fig. 34e. Note the erosion of the right internal auditory meatus ($\leftarrow$).

The percutaneous method of angiography was introduced in England in 1946 and the steady increase in the number of cases investigated by the method is obvious, as is the great importance it has assumed in the diagnosis of intracranial lesions.

Indications. The indications for carotid angiography are summarized in the following table:—

A. *Intracranial expanding lesions:*

1. Tumours.
2. Abscess.
3. Granuloma.

B. *Vascular lesions:*

1. Aneurysm.
2. Angiomatous malformation.
3. Subdural hæmatoma and extradural hæmatoma.
4. Intracerebral hæmatoma.
5. Embolus.
6. Thrombosis.

It is not possible in a work of this kind to deal exhaustively with the subject of cerebral angiography, but some of the important points elaborated during the work of the last few years will be briefly discussed.

In the diagnosis of *tumours* angiography is, in many cases, superior to other methods of investigation, such as ventriculography, because it provides not only localization of the tumour but also a pathological diagnosis of the type of tumour. Thus the surgeon may learn as a result of an angiogram the exact site, size and pathological nature of the tumour with which he is dealing. Further, he will be shown its vascularity and blood supply, i.e. virtually all the information he could possibly desire before operative exposure and removal. This of course does not imply that angiography is the investigation of choice in all cases and that pneumography can be dispensed with. The two investigations are complementary and the method chosen depends in each case on the situation and nature of the lesion. In one case angiography will be virtually useless and pneumography of great value; in another the reverse may hold. In many cases both investigations may have to be undertaken, each method individually providing additional information not obtainable by the other.

Angiographic evidence of an expanding lesion is best shown in hemisphere tumours. With a tumour large enough to produce

clinical signs there will nearly always be some displacement of the anterior cerebral artery across the midline. Such displacement, if more than a few millimetres, is virtually diagnostic. The exact site of the tumour will be further suggested by local stretching of arteries in its area. Thus, a temporal tumour will displace the middle cerebral vessels upwards in an arc.

Tumours in the midline and in the basal ganglia region, however, will not be so well shown by angiography because they are located well away from, and deep to, the main vessels, and because the anterior cerebral artery may remain central. However, it has been recently shown that these tumours may produce characteristic deformities of the deep cerebral veins seen in the late phlebogram films (Johansen, 1953, Richter, 1953).

The pathological diagnosis of intracranial tumours by angiography depends on the increased vascularity and abnormal vascular patterns seen in certain kinds of intracranial neoplasm. Thus, a *malignant glioma*, when highly vascular, shows an irregular ill-defined area of abnormal little sinusoids filled with contrast. *Meningiomas*, in a high proportion of cases, show as a diffuse homogeneous opacity, the so-called "meningioma blush" or "smear". The angiogram may also show hypertrophied meningeal arteries or external carotid branches feeding the tumour, a diagnostic feature.

Secondary deposits may show as irregular collections of sinusoids and pathological vessels, similar to those seen in malignant glioma. In deposits, however, the lesion is usually well rounded and circumscribed and multiple discrete lesions may be seen.

Hæmangioblastoma is another tumour which has a characteristic vascular pattern, but this will be discussed below under vertebral angiography. The proportion of intracranial tumours which show evidence of pathology of the type described varies in different series. More than half the gliomas can be expected to show some evidence of their pathological nature. Naturally this is best seen in the more malignant gliomas and implies a poor prognosis. The less malignant gliomas may show no evidence of pathological vessels but they will produce evidence of their presence as expanding lesions in the manner described above. About two-thirds of the meningiomas will show a characteristic angiographic picture; the rest, however, will merely produce evidence of the presence of an expanding lesion. Many deposits will also show some evidence of a pathological circulation but this will depend upon the vascularity of the particular deposit.

Turning now to the discussion of intracranial *vascular lesions*, let us first consider *aneurysms*. The ready demonstration of these lesions by percutaneous angiography has considerably influenced the treatment of subarachnoid hæmorrhage, their commonest mode of presentation. Present views favour surgical rather than medical treatment of this serious clinical emergency, though the method of surgical treatment remains controversial. At a recent discussion on the subject at the Royal Society of Medicine, Norlen (1952) and Falconer (1952) produced evidence in favour of direct intracranial attack upon aneurysms, whilst Jefferson (1952) favoured the more conservative carotid ligation. It appears that it will be some years before conclusive evidence can be supplied in favour of a particular mode of treatment. Angiography has provided a relatively simple means of demonstrating the anatomical situation of the aneurysm and has thus stimulated surgical attempts to improve the serious mortality and morbidity of this grave condition.

Angiomatous malformations are another group of intracranial lesions where diagnosis and treatment have been profoundly affected by the influence of angiography. Until recent years few could present any large experience of verified cases of angioma. The classical monograph of Cushing and Bailey (1928) on the subject was based on a series of only 15 cases. It is now realized that angiomas are one of the commonest types of intracranial lesion. Among a large series of angiograms performed for the investigation of all types of intracranial conditions angiomas are consistently found to be present in some 5 per cent, and the writer has personally seen over 100 cases in the last six years. A small, though appreciable, proportion of these cases have presented with subarachnoid hæmorrhage, so that although aneurysm remains far and away the most common cause of this condition, hæmorrhage from an angioma is a diagnosis which may also have to be considered. Since larger numbers of these lesions have been demonstrated, attempts at surgical removal have increased. Provided the malformation is not too large and inaccessible successful operative removal can be performed in many cases (see Figs. 36a and b).

Subdural hæmatomas can now be accurately diagnosed by angiography. Films taken in the antero-posterior plane show a characteristic avascular area between the brain and the skull vault (see Fig. 37).

Thrombosis of the internal carotid artery has long been recognized

by Moniz and other continental writers as presenting a neurological syndrome. Since the widespread use of angiography its importance has also been realized in this country. The diagnosis must be considered in any obscure or remittent case of progressive hemiplegia. The majority of cases show a characteristic radiological picture consisting of a complete block of the internal carotid artery about 1 cm. from its origin (see Fig. 38). About 20 cases of this condition have been encountered among the writer's material. Angiographic studies have shown that the vessels on the affected side may be fed not only from the Circle of Willis but also by direct anastomoses between the ophthalmic artery and external carotid artery (via the maxillary artery). Extra blood may also reach the affected hemisphere from occipital-vertebral anastomoses contributing to an increased basilar blood flow. There is then retrograde flow along the posterior communicating artery to supply the affected hemisphere.

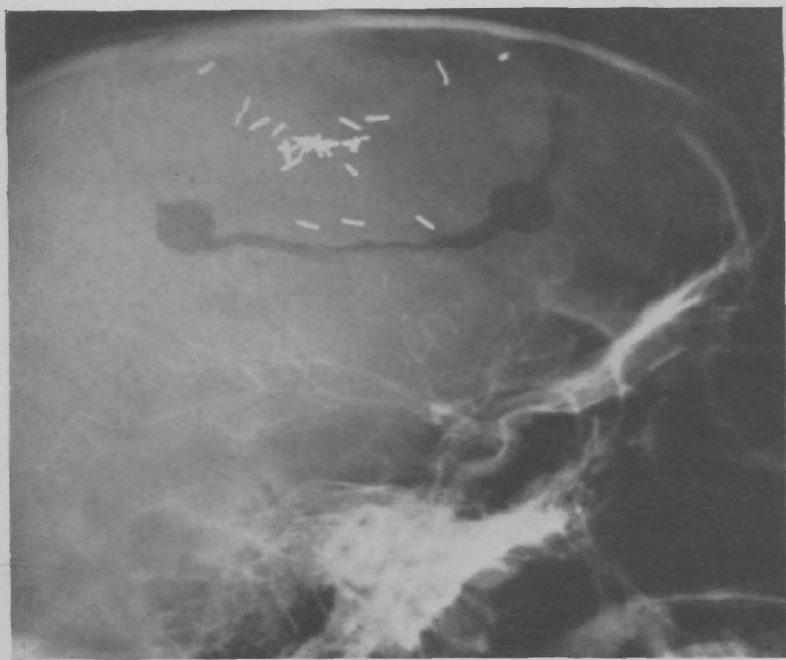
Thrombosis of the common carotid artery is a much rarer condition. The clinical findings are similar to those of thrombosis of the internal carotid artery. Only one case has been seen in the writer's series. Thrombosis of the external carotid artery is also rare, and again only a single personal case has been encountered. The latter condition does not give rise to symptoms and is usually found accidentally in a patient being investigated for an intracerebral lesion.

Vertebral Angiography

The routine adoption of percutaneous carotid puncture naturally led to attempts to widen the scope of cerebral angiography to include the vertebral artery. Percutaneous vertebral angiography is more difficult than carotid angiography owing to the depth and inaccessibility of the vessel and to its smaller and more variable size. However, the procedure is now practised with a promising degree of success at a number of centres (Sugar *et al.* 1950, Lindgren, 1950b, Sutton and Hoare, 1951). In experienced hands the percutaneous method of vertebral angiography provides successful angiograms in over 90 per cent of the cases investigated. (Sjogren, 1953). For details of the technique and complications the articles mentioned above should be consulted. In addition to the percutaneous method of vertebral angiography a method based on catheterization of the radial artery has been developed by Radner (1950). In his hands this has proved highly satisfactory and successful visualization of the intracranial vessels has been



(a)



(b)

FIG. 36. (a) Small parasagittal angioma showing large dilated draining vein.
 (b) After operative removal, no angiographic evidence of tumour remains.

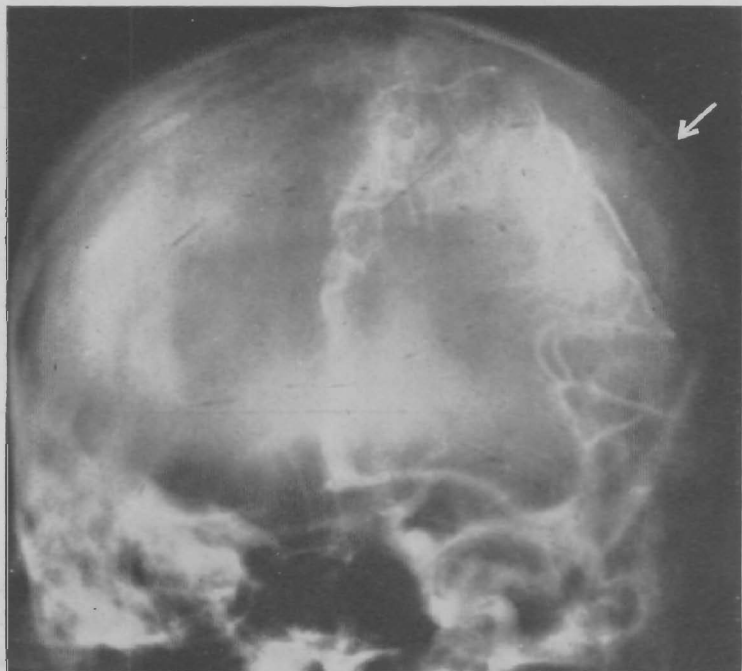


FIG. 37. Subdural hæmatoma. Antero-posterior film showing the pathognomonic avascular area between the skull vault and the cerebral vessels.

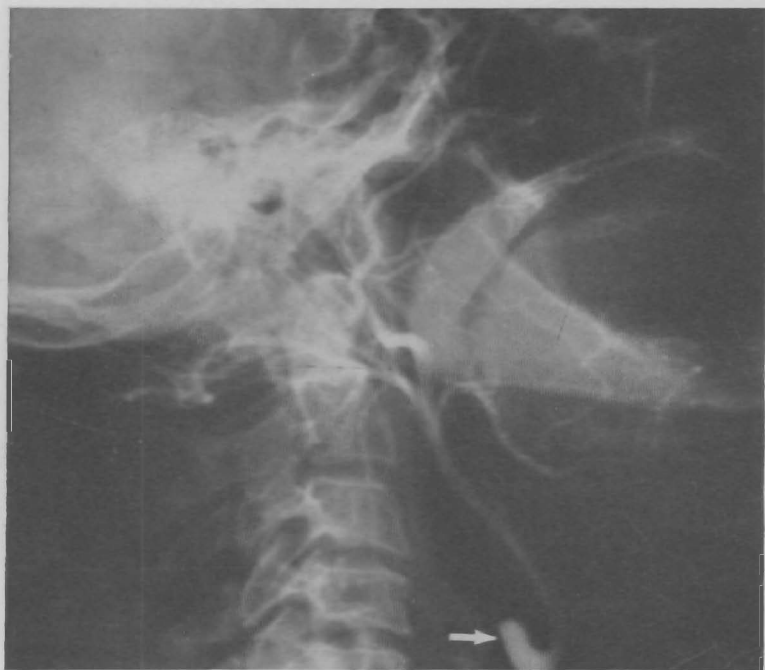


FIG. 38. Thrombosis of internal carotid artery in the neck. This is the common site, about 1 cm. from the vessel's origin. The external carotid artery is filling normally.



(a)



(b)

FIG. 39.

- (a) Vertebral arteriogram. Late arterial and capillary phase. A tumour growing on both sides of the tentorium is demonstrated ($\leftarrow$). Note the characteristic "blush" suggesting meningioma.
- (b) The tumour is found at autopsy. The patient died after ventriculography and before operation could be undertaken.

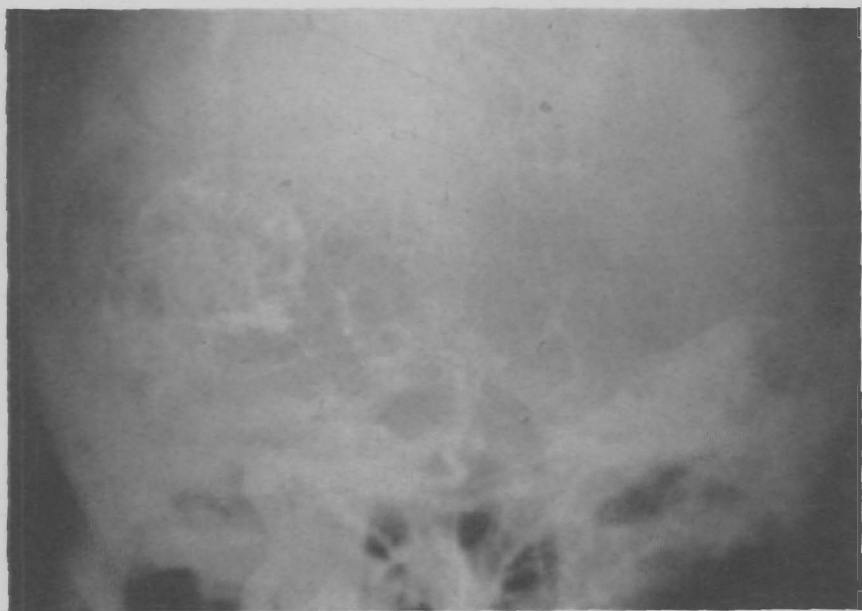


FIG. 40. Vertebral angiogram. Large cerebellar hæmangioblastoma shown in frontal view.



(a)



(b)

FIG. 41

- (a) Vertebral angiogram. Large aneurysm arising from the basilar artery at its termination.
- (b) Vertebral arteriogram. Huge angioma fed by the posterior cerebral artery.

(Courtesy of the Editor, *Arch. Mex. Hosp.*)



FIG. 42. Dural sinus phlebogram. The sagittal sinus is draining entirely to the right side. The Polythene catheter has been inserted into the sagittal sinus through a burr hole. An oblique film is taken to show the whole length of the sinus.

achieved in over 95 per cent of cases. Our own limited experience of this method, however, has been less promising and we feel that considerable practice and experience is necessary, as with the percutaneous method, before consistently good results can be obtained.

The indications for vertebral angiography may be classified as:—

(A) expanding lesions.

(B) vascular lesions.

To consider the expanding lesions first: it is probably true that the usefulness of the method is far less than with supra-tentorial tumours, and in many cases it is inferior to pneumography and positive contrast ventriculography for tumour localization. Pontine tumours for instance cannot be accurately diagnosed by vertebral angiography, and their localization and diagnosis is better achieved by the alternative methods. That vertebral angiography can prove of considerable assistance in posterior fossa tumours is however exemplified by the accompanying illustrations demonstrating type diagnosis of tumours. They show characteristic changes in a meningioma (Fig. 39) and in a hæmangioblastoma (Fig. 40) respectively.

Large cerebello-pontine angle tumours may be well shown by vertebral angiography as in a case recorded by Sutton and Hoare (1951). That the method may prove diagnostic even with smaller lesions is claimed by Olsson (1953) in an analysis of 14 acoustic tumours which were thus investigated.

Whatever the merits or demerits of vertebral angiography in the diagnosis of posterior fossa tumours there can be no doubt of its immense value in the diagnosis of posterior fossa vascular lesions. The method in fact offers the only pre-operative or pre-autopsy method of diagnosing such lesions.

Fig. 41a shows a basilar aneurysm arising at the termination of the artery.

A number of cases of angioma of the posterior fossa, hitherto considered an extremely rare lesion, have now been personally encountered. Some of these have been recently described (Sutton, 1952) and others are included in a series of cases reported by Logue and Monckton (1954). It is interesting that two cases which are recorded in our series had received clinical diagnoses of pontine glioma.

In addition a number of cases of occipital angioma fed mainly or partly by the vertebral artery have been demonstrated (Fig. 41b).

Dural Sinus Phlebography .

In certain types of cases it may be necessary to consider the diagnosis of occlusion or thrombosis of the superior longitudinal or lateral sinuses. The normal cerebral angiogram does not show these structures adequately and consistently enough for these special diagnostic purposes and a special technique is therefore required for their investigation (Ray, Howard and Dotter, 1951). Cases of so-called "toxic" or "otitic" hydrocephalus fall into this group. In these cases, which are associated with raised intracranial pressure and even papilloedema, the ventricular system will be shown by pneumography to be normal. The possibility that the raised pressure may be due to increased venous pressure following occlusion of a main sinus has to be considered, and dural sinus phlebography may conclusively settle this problem. Again, in the case of tumours such as meningioma involving the longitudinal sinus a dural sinus phlebogram will enable one to determine whether or not the sinus is invaded and blocked.

The technique is as follows:—

The neurosurgeon makes a parasagittal frontal burr hole in the theatre and through this inserts a polythene catheter into the sagittal sinus. The patient is then transferred to the X-ray Department and serial films are taken during and after the injection of 10 ml. of 35 per cent Diodone. This gives good direct visualization of the superior sagittal sinus and its draining lateral sinus. The type of result obtained is illustrated in the accompanying figure Fig. 42.

The Spine : Myelography : Discography

Plain radiography of the spine may be of considerable assistance in the investigation of many cases with neurological symptoms. It is essential in all cases of cord compression and root compression. By its aid such congenital lesions as spina bifida; the Klippel-Feil deformity, congenital hemivertebrae, or various bone dystrophies may be demonstrated. Evidence of tuberculous infection of the spine will be shown, or the presence of neoplasms, primary or secondary. Paget's disease, or vertebral haemangioma may be diagnosed. Finally evidence of an intraspinal tumour may be seen. Such evidence consists of:—

- (1) Widening or erosion of the vertebral pedicles, best seen in the dorsal or lumbar region on antero-posterior films (Fig. 43).

- (2) The local unilateral enlargement of an intervertebral foramen seen in cases of dumb-bell tumour.
- (3) A paraspinal mass associated with a dumb-bell tumour (best seen in the thoracic region).
- (4) Erosion of the vertebral body from behind, most commonly seen with a large spinal neurofibroma.
- (5) Intraspinous calcification, a rare finding, but almost diagnostic of spinal meningioma (Grey, 1942). The writer has also seen intraspinal calcification due to protrusion of a calcified degenerate disc.

A lesion which is treated more fully elsewhere but in which the radiological findings are of great importance is disc prolapse and degeneration. The importance of this as the commonest cause of sciatica is now well established, but only in very recent years has the picture of cervical spondylosis and its considerable importance in producing neurological symptoms become clear.

The radiological evidence of disc degeneration is:—

- (1) Narrowing of the intervertebral disc space.
- (2) Adjacent osteophytosis of the vertebral margins.
- (3) Sclerosis of the vertebral margins.
- (4) Disc calcification.
- (5) The "vacuum phenomenon": an apparent linear gas space which may be seen in a degenerated disc, usually in the lumbar region.
- (6) Local abnormal mobility, or fixity.

Plain X-rays will nearly always provide some evidence of the presence of a disc lesion. On the other hand, even gross radiological evidence of disc degeneration may be present without any clinical evidence of neurological complications. The clinical and radiological evidence therefore must be carefully correlated before a disc lesion is accepted as a cause of the symptoms. In many cases it may be necessary to perform the additional investigation of myelography before a definite decision can be made. The importance of the myelographic evidence in proving the diagnosis of cervical spondylosis as a cause of cord lesions is discussed by Sir Russell Brain in another section.

It has been stated above that plain X-rays may provide evidence of the presence of an intraspinal tumour. In this respect it is important to recognize "pedicle erosion" (Fig. 43). In the dorsal

and lumbar region the pedicles of the vertebræ appear on antero-posterior films of the spine as ovoid shadows: this represents the cortex of the pedicle seen end-on. An intraspinal expanding lesion causes pressure on the pedicles and the normal convex inner margin becomes flattened and eroded (Fig. 43). On the X-ray this is first manifested as a loss of the normal medial convexity and a widening of the interpeduncular distance. The latter

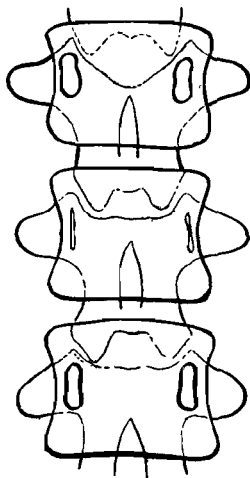


FIG. 43. Antero-posterior diagram in spine showing pedicle erosion at the level of a spinal tumour.

can be demonstrated by direct measurement and reference to specially constructed charts.

Further evidence of the presence of an intraspinal tumour may be provided by the demonstration of local expansion of an intervertebral foramen or of erosion of the back of a vertebral body. Both these signs are seen with neurinomas, though the latter may be seen with other rarer lesions such as dermoids.

Diastematomyelia is a rare lesion of which an increasing number of cases are now being reported. It consists of a congenital malformation of the spine in which a bony spur extends from the back of a vertebral body to the posterior arch, usually in the lower dorsal region. The spur actually transfixes the cord which is therefore bifid in the affected region. Neurological signs develop as growth proceeds owing to traction upon the cord. The bony spur

may be difficult to demonstrate by plain X-rays but can be well shown by tomography (Cowie, 1952). Myelography will show diagnostic appearances. Occasionally, as in a case seen personally, there may be an associated congenital tumour such as a dermoid, which will confuse the diagnostic issue. In addition to the bony spur the plain X-rays may show local widening of the interpeduncular distances.

Myelography

Various contrast media have been used in the past for myelographic investigations. Lipiodol was used for some time before its tendency to cause local adhesions and arachnoiditis led to its abandonment by most workers. Today the most widely used contrast medium is Ethyl Iodophenylundecylate (known under various trade names as Pantopaque, Myodil etc.). This is a much more innocuous medium than Lipiodol and is used in larger amount (5 ml. is the quantity usually injected). Some observers consider Myodil to be completely harmless and do not remove the medium after the investigation. Others however, consider it advisable to aspirate the contrast immediately after the examination. Although this medium is the one most widely used for myelography some workers, particularly in Sweden, prefer to use gas contrast. The latter medium requires an examination which is technically more complicated and difficult, and may necessitate concomitant tomographic examination of the spine (Oden, 1953).

Diodone has also been used in Sweden for the investigation of the spinal subarachnoid space. This latter medium enables the most beautiful diagnostic results to be obtained but owing to its hypertonicity a preliminary spinal anaesthetic must be given before its use, and the medium can therefore only be used for examination of the lumbar region. The necessity for this greatly limits the scope of the method.

Technique. It is only proposed to describe here the method of myelography using Ethyl Iodophenylundecylate. Five mls. of the contrast medium are injected into the subarachnoid space. We prefer to inject the medium at lumbar puncture in the ward or operating theatre before the patient is brought to the X-ray department. Some workers, however, inject by the cisternal route in the X-ray department. In cases where a definite tumour causing a subarachnoid block has been shown, injections are occasionally made both cisternally and by lumbar puncture in order to delineate both the upper and lower margins of the tumour.

In the X-ray department the patient is placed prone upon the tilting table and the medium is confirmed by screen examination to be pooled in the lumbar region. Unless only the lumbar area is to be examined, the patient is then tilted head downwards so that the contrast (which is heavier than cerebrospinal fluid) flows down towards the cervical region. If no block is encountered, the contrast is pooled in the cervical zone which is carefully examined. It is then tilted back to the lumbar region by reversing the above procedure. The whole process is carefully controlled by observation under the fluorescent screen, and spot films of suspicious

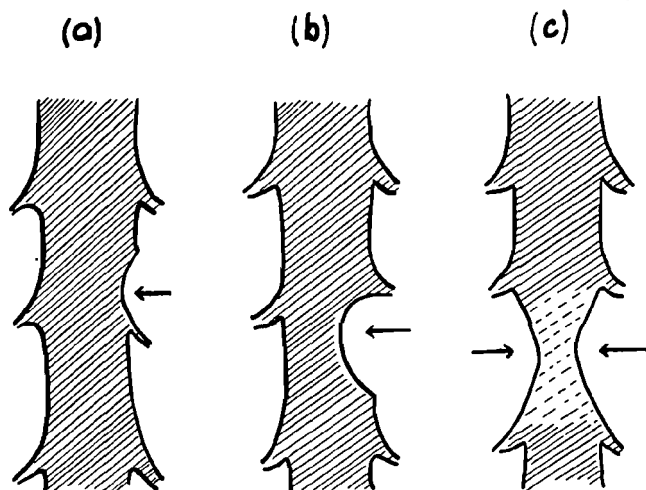


FIG. 44. Lumbar disc lesions as shown by myelography in antero-posterior views. (a) and (b) lateral disc protrusions. (c) Central protrusion.

areas, or of the level of a block, are taken. It is important to obtain films in both lateral and anteroposterior projections, and this is absolutely essential for the diagnosis of such lesions as centrally placed disc protrusions. It is equally important that myelography should not be performed within ten days of a previous lumbar puncture. As explained in the discussion on encephalography a lumbar puncture is often followed by a seepage of cerebrospinal fluid into the potential subdural space. A recent lumbar puncture is nearly always the cause of a subdural injection of the contrast medium. Such subdural injections give rise to puzzling radiological pictures and make subsequent diagnosis more difficult.

Indications. Myelography will accurately demonstrate the majority of disc protrusions. The appearances seen in the antero-posterior radiographs with different types of lumbar disc lesions are illustrated in the accompanying diagrams (Fig. 44).

With spinal tumours, myelography will demonstrate the exact level of the tumour and will also give some information as to its nature and anatomical location. Thus it is usually possible to

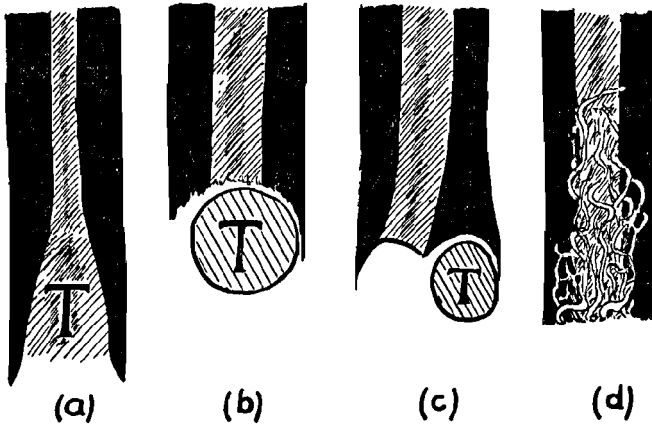


FIG. 45. Characteristic appearances in various types of spinal tumour shown diagrammatically.

- (a) Intramedullary tumour. Note diffuse enlargement of the cord.
- (b) Extradural tumour: extradural.
- (c) Extradural tumour: intradural. Note deviation of the cord impression.
- (d) Angiomatous malformation. Note impressions due to enlarged vessels.

differentiate between intramedullary and extradural tumours. Extradural tumours can again be sub-typed as either intradural or extradural.

The typical radiological appearances in these different types of spinal neoplasm are illustrated in the accompanying diagrams (Figs. 45a, b and c). Another type of lesion which may be revealed by myelography is an angiomatous malformation. The characteristic worm-like enlarged vessels are well shown as negative shadows in the contrast column (Fig. 45d). It should be remembered however, that similar appearances can occasionally be produced by engorged vessels adjacent to a tumour.

Finally myelography will demonstrate various other lesions causing cord compression such as extradural abscess, kinking of the cord at the level of scoliosis or kyphosis, and meningeal adhesions.

Discography

In recent years Lindblom (1950) has perfected a technique for visualization of the nucleus pulposus in the lumbar region by direct injection of the disc space, after trans-spinal needling. It is possible by this method to provide direct evidence of disc injury and protrusions. The method, however, has not yet been widely used, as many observers feel that there is some danger of damaging an otherwise normal disc. The diagnostic results obtained appear to be eminently satisfactory in demonstrating disc protrusions.

Miscellaneous Lesions of Neurological Interest

Myasthenia gravis has long been known to have some association with abnormalities of the thymus and it is being increasingly realized that thymic tumour is not uncommon. Seybold *et al.* (1950) reviewed 45 patients with tumours classified as thymic. They found that 75·6 per cent of patients with thymoma have myasthenia gravis and that 15 per cent of their patients with myasthenia gravis had thymic tumours. The demonstration of thymic tumours pre-operatively depends on detailed X-ray examination by an observer familiar with the problems involved. A thymic tumour usually lies in the anterior mediastinum but has occasionally been discovered posteriorly in the thorax. Although most frequently seen anterior to the arch of the aorta it may be found at any level down to the diaphragm. The tumour is commonly rounded or ovoid and well delineated, but in some instances the mass may be flat and closely attached to the anterior surface of the pericardium. In this latter case it may be very difficult to demonstrate radiologically. The radiologist cannot be confident that no tumour is demonstrable unless he has (a) taken films in postero-anterior and lateral projections; (b) screened the patient; (c) taken tomographic films in the lateral plane, and in some cases in the anteroposterior plane also. It is not generally realized that an appreciable proportion of thymic tumours contain sufficient calcium to be apparent radiologically (13 out of 45 cases in Seybold's series). The writer has recently seen two such cases of calcified thymoma (see Fig. 46).

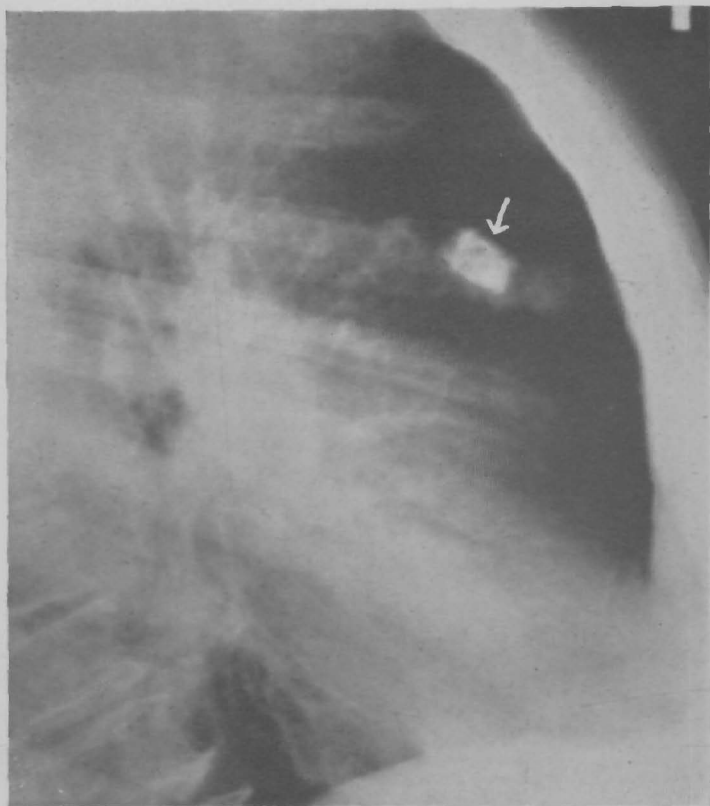


FIG. 46. Thymoma in a case of myasthenia gravis, showing marked calcification in the anterior mediastinal tumour.

Neuropathic Joints are well known to occur in tabes and in syringomyelia, and more rarely in other neurological conditions. It has recently been shown that neuropathic joints are not uncommon in diabetics. The first metatarso-phalangeal joints, or the mid-tarsal joints, are the ones commonly affected (Martin, 1953). Neuropathic joints have also been noted in the rare condition of congenital absence of pain sense.

Tumours of the Glomus Jugulare have been the subject of considerable attention in recent years and are now being recognized in increasing numbers. Six cases were presented by Henson, *et al.* (1953) and five by Hooper (1955). The clinical symptoms are varied but usually include such features as a long history of pulsating tinnitus or deafness, a vascular polyp presenting through the tympanic membrane, cranial nerve paralyses, or signs of raised intracranial pressure suggesting a posterior fossa neoplasm. Radiographic changes are present in a proportion of these cases. The most important of these is erosion of the petrous portion of the temporal bone, but sclerosis of the mastoid and enlargement of the jugular foramen are also described. These tumours are extremely vascular and angiography of the external carotid artery sometimes, but not always, demonstrates them well.

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CHAPTER 14

INTRACRANIAL TUMOURS

by

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It is a little over 20 years since Cushing (1932) published his monograph on "Intracranial Tumours", and included an analysis of what was then the largest series of cases. The percentage incidence of the various groups of tumours may not have represented their natural incidence, owing to selection. So that this possible error may be corrected, in the following table are listed the major groups of tumour, and their percentage incidence, as derived from publications of Cushing (1932), Cairns (Cairns and Jupe, 1951) and Olivecrona (1952). It is likely that the mean of these figures approximates to the natural incidence, having regard to the geographical situation of the centres concerned and to the large numbers of cases. Cushing's totalled 2,023, Cairns 738 (1927-1937 inclusive) and Olivecrona 4,188; the last named appears to be the largest series ever published, or likely to be published from one centre in view of the increasing number of neuro-surgical centres which are being set up in most countries.

THE PERCENTAGE INCIDENCE OF VERIFIED INTRACRANIAL TUMOURS

<i>Variety</i>	<i>Cushing (1932)</i>	<i>Cairns (1951)</i>	<i>Olivecrona (1952)</i>
Glioma . . .	42·6	47·0	47·0
Meningioma . . .	13·4	14·5	19·2
Pituitary Adenoma . . .	17·8	10·3	8·7
Acoustic Tumour . . .	8·7	6·0	8·6
Blood-vessel Tumour . . .	2·0	4·6	5·1
Congenital Tumour . . .	5·6	4·7	3·0
Metastatic . . .	4·2	7·6	3·5
Granuloma . . .	2·2	1·3	1·3
Miscellaneous . . .	3·5	3·8	1·0

Certain groups are not strictly comparable, but this can have little influence on the general significance of the comparisons. Thus, in Olivecrona's list, the word "acoustic" does not appear, and "neurinoma" alone is listed; the percentage 8.6 therefore includes relatively rare tumours such as those of the trigeminal root and ganglion. He also includes "aneurysm 1.9 per cent" which group and figure has been entirely omitted here, without making any correction. The blood-vessel tumours for convenience include the arterio-venous malformations and hæmangioblastomas; the congenital tumours include Rathke-pouch tumours, epidermoids, cholesteatomas and teratomas; and the miscellaneous group comprises amongst others colloid cysts, papillomas and cranial tumours. The outstanding discrepancies are meningioma, high in the Swedish figures; pituitary adenoma, high in the American figures; and the steady rise in the group of blood-vessel tumours as the years pass, doubtless reflecting the introduction and increasing employment of angiography in the diagnosis of vascular malformations. Another discrepancy revealed in the original publications is the much greater incidence of Rathke-pouch tumours in Cushing's series. There were 92 in his total of 2,023 tumours, and 74 in Olivecrona's series of 4,188.

Skull

Epidermoid cysts may occur within the tables of the calvarium, arising in the diploë, and usually display a characteristic appearance in the radiogram, there being a central loss of bone surrounded by a clear-cut, dense, scalloped margin. The bone may be "expanded" so that there is an external palpable lump, and occasionally complete erosion of the inner table allows the cyst to become firmly adherent to the dura mater (Courville 1946, 1947; King 1939; Rand and Reeves 1943). A small group of these tumours has particular importance; they arise in the petrous portion of the temporal bone and by direct pressure produce a progressive facial palsy. Removal of the tumour may on occasion allow the palsy to recover (Jefferson and Smalley 1938; Pennybacker 1944-1945).

Chordoma may occasionally arise in the skull and its site of election is the basi-sphenoid. It may project backwards into the posterior fossa to simulate a clivus meningioma; or it may extend laterally into the cavernous sinus and middle fossa, or upwards as a supra-sellar mass and is liable to be mistaken for an atypical pituitary adenoma. To the naked eye it somewhat resembles

cartilage and microscopically mimics notochordal tissue. Whether the tumour arises from persistent remnants of the notochord or from the de-differentiation of cells derived from that embryonic structure remains uncertain. There are particular areas in which the tumour most frequently arises. It is commonest at either end of the spinal axis. Birrell (1952) analysed the published cases, and records the distribution as follows: cranial 105, vertebral 86, sacro-coccygeal 143. The tumour is normally slowly growing, but rarely amenable to total removal. Long post-operative survivals have been recorded and metastases are rare (Gardner and Turner 1941, Wood and Himadi 1950).

Myeloma usually affects the skull as part of the generalized state of myelomatosis, X-ray examination revealing numerous areas of osteolysis as in carcinomatosis. Occasionally a solitary tumour arises which may cause an external lump, and may extend into the cranium giving rise to neurological disorder. Radiograms reveal bone destruction with no osteoblastic reaction and sometimes with a trabeculated appearance. The opinion is now held that such solitary tumours, often termed plasmacytoma, are but the initial manifestation of myelomatosis and that sternal puncture will usually reveal this diagnosis; alternatively, that the generalized disease will become evident within a few years. Russell (1951) has recorded a case in which necropsy revealed no other tumour deposits, though the bone marrow was not examined microscopically. Clarke (1954) has recently made a valuable review of cranial and intracranial myeloma which he divides into three groups. The first is characterized by cranial nerve palsies, the abducens being the most frequently involved, the tumour arising in the base of the skull. The second group comprises those in which the clinical picture is that of an intracranial tumour; usually the myeloma arises from bone, but very occasionally it arises from non-osseous tissue, and a case is recorded in which the tentorium was the site of origin. In the third group are those cases in which the tumour is orbital; it may be primarily intraorbital in origin growing either from the wall or the contents, or the tumour may secondarily encroach upon the orbit. Treatment is discussed.

Eosinophilic Granuloma may affect the skull as well as other bones, and may be single or multiple. It causes a diffuse tender swelling with radiological evidence of bone destruction, the margin usually being ill-defined. Although relatively uncommon, reports of the condition have frequently appeared in recent literature, and its recognition is important as it may simulate a chronic pyogenic

lesion. It more commonly affects young persons, and is related to Letterer-Siwe and to Hand-Schüller-Christian diseases; there may be an associated purpura (Swann and Williams 1953). Occasionally the mass may invade the brain. The lesion is amenable to surgical removal and to irradiation, and indeed may subside spontaneously (Baker and Fisher 1948, Hill 1949).

Osteoma of the skull is rarely of importance unless it involves the fronto-ethmoidal and orbital regions. The problems involved were first emphasized by Cushing (1927). Arising in the frontal or ethmoidal sinuses they may reach a very large size, and by isolating portions of mucosa, and by erosion of bone and of dura mater, may pave the way for the development of mucocoele, aerocoele and intracranial infection. The bony tumour may grow into the orbit and cause displacement of the eyeball. Begley and Hallberg (1950) have briefly reviewed a large series of cases, and more recently Kessel (1953) describes nine cases in detail.

Fibrous Dysplasia of bone may affect the skull as an isolated lesion (monostotic). In its severe and more diffuse form (polyostotic) it is characterized by multiple bony lesions, abnormal cutaneous pigmentation and endocrine disturbances, and is frequently referred to as Albright's syndrome. Isolated lesions in the skull are of radiological importance as they may be mistaken for meningiomas. Feiring, Feiring and Davidoff (1951) describe five cases of the monostotic variety, in three of which the presenting symptom was unilateral proptosis, and in the fourth it was unilateral optic atrophy; the fifth patient complained of a large lump in the temple. The literature is fully reviewed, the relation between monostotic fibrous dysplasia and leontiasis examined, and the differential diagnosis discussed.

Glomus Jugulare Tumour. In 1945 Rosenwasser reported the case of a tumour of the tympanic cavity which resembled in structure the small mass of tissue lying in the dome of the bulb of the internal jugular vein, described by Guild (1941) and to which he gave the name of glomus jugulare. Thereafter frequent references by otologists indicated that vascular tumours of the middle ear often regarded as hæmangioma or endothelioma were of this nature, and occurred more commonly than at first was believed. Latterly it has been shewn that such tumours have more than an otological interest, for they may erode the petrous bone and give rise to neurological manifestations. Henson, Crawford and Cavanagh (1953) describe in detail six such cases. The duration of the illness varied between four and 30 years. In each an aural polyp

(usually very vascular) was present and several cranial nerves were involved from the trigeminal downwards; in two there were signs of cerebellar disorder; in four a bruit was detected on auscultation. X-rays of the skull shewed bone destruction in only two. An important feature of diagnosis is the detection of the aural polyp and its biopsy. If the tumour is extensive, surgery has little part to play in its eradication, though suboccipital decompression may be helpful as a palliative measure. Irradiation is the treatment of choice. Bickerstaff and Howell (1953) state that external carotid angiography may reveal the abnormal vascularity of the tumour. In an analysis of 49 recorded cases they found that neurological symptoms succeeded aural after an interval of from 10–20 years in 20; neurological and aural manifestations occurred concurrently in 17, and in only four were neurological symptoms noted before aural. They suggest that the precise situation of the glomus may determine the chronological sequence of events.

Meninges

Meningioma. The pathology of this group of intracranial tumours has recently been reviewed by Russell (1950). They are derived from nests of arachnoid cells in the dural mater, from arachnoid villi, and occasionally from the stroma of the choroid plexus. Many histological types have been described and Russell adopts the following scheme put forward by Courville (1945).

1. *Syncytial*: composed of sheets of polygonal cells separated by vessels and collagen; it accounts for about one half of all meningiomas, and corresponds to the meningiothelioma of some writers.

2. *Transitional*: in which the cells tend to be orientated in whorls, some cells being spindle-shaped and containing fibroglial fibrils. When this pattern is exaggerated so that the whorls are more tightly spun, the centre may undergo hyaline degeneration and become calcified, giving rise to psammoma-bodies.

3. *Fibroblastic*: where there is a rich deposition of collagen fibres with intervening spindle cells. This is sometimes called a dural fibroblastoma, but Russell points out that meningiomas arising from the pia of the spinal cord and within the ventricles are usually of this type.

4. *Angioblastic*: the tumour contains numerous capillary blood-spaces separated by polygonal cells which may be foamy and may shew mitoses; there is a rich reticulum network. It is this type of highly vascular meningioma which is likely to occur about the

Torcular, though they may be found arising from the pia. Histologically, these tumours may be identical with the Lindau hæmangioblastoma of the cerebellum, and the view has been expressed that the two tumours are in fact one and the same. Russell reviews the arguments for and against the separation of these tumours, and concludes that there is sufficient evidence to maintain their separate identities.

5. *Sarcomatous*: although a meningioma may recur—and generally does so—if it is incompletely removed, the recurrence usually maintains its original histological structure. On occasion the primary operation may have been quite complete to the naked eye, as in convexity growths in which the dural attachment can be completely excised with the tumour; recurrence of a benign nature may then occur by reason of minute fragments being shed in the bed of the tumour during removal (Turner, Craig, Kernohan 1942). But occasionally the recurrence may be more rapidly growing and show unmistakable histological evidence of malignancy. Finally, a growth when first removed may resemble in its general appearance a meningioma, but may be found on histological examination to be a highly cellular fibrosarcoma. A few records have appeared in the literature of malignant meningiomas which have given rise to blood-born metastases, and the authenticity of some of these examples is now accepted.

Chistensen and Lara (1952) described 25 cases of intracranial sarcoma ranging in age from nine months to 67 years. They were grouped as fibro-sarcomas, spindle-celled and undifferentiated sarcomas. Operation was carried out in all. In the five cases of fibrosarcoma the removal was complete, and one patient was alive after 14 years and two for shorter periods. In the nine cases of spindle-celled sarcoma total removal was possible in seven; one patient was alive after 12½ years, and one alive after one year; the others all died from recurrences. There were 11 cases of undifferentiated tumour, and all these patients died within three years.

Hyperostosis. The stimulus to new-bone formation is a characteristic of some meningiomas which has been long recognized, and is of the greatest value in radiological diagnosis. It is particularly liable to occur in parasagittal tumours, and in those arising from the sphenoid. The hyperostosis is not necessarily invaded by the meningioma, though it often is, and tumour cells may even penetrate the pericranium and muscle. Such invasive cells do not shew any histological malignant changes. The cause

of the new bone formation remains problematical. It has been suggested that where there is no invasion, there has been a stimulus to bone formation by the effect of stretching of the periosteal layer of the dura by the distortion of the tumour. Bailey (1940) suggests that the meningioma derives its polygonal epithelioid cells from the surface-covering cells of the arachnoid, and that its fibroblastic or spindle-shaped cells are stromal in origin, corresponding to the supporting cells of the arachnoid. The hyperostosis may then be the expression of a stroma formation in bone by the stimulated periosteum.

The predilection of the meningiomas for particular sites, and the consequent syndromes to which they give rise have been clearly set out by Cushing and Eisenhardt (1938) in their famous monograph. These groupings are now fairly well known although some of the less commonly occurring need emphasis.

Perhaps the most difficult to diagnosis are those small anterior basal meningiomas which implicate one optic nerve. Progressive failure of vision of one eye may be so slow and the optic disc may shew so little evidence of atrophy that procrastination before taking steps to arrive at an accurate diagnosis is an easy path. In the absence of an ocular cause, it is safer to assume that progressive unilateral visual failure is due to optic nerve compression until the contrary has been proved by investigation or by exploratory operation. Such investigations must include careful examination of the visual fields and particularly for a scotoma which can easily pass undetected. Mooney and McConnell (1949) and Guillaume and Masseboeuf (1947) stress the importance of a scotoma as evidence of pressure on the optic nerve. The tumour need not be a large one and may arise from the anterior clinoid process (Uihlein and Weygand 1953) or from the margins of the optic canal. Craig and Gogela (1950) point out how easily such tumours may escape detection at operation. It is in cases of tumour compressing the optic apparatus that air-encephalography is valuable if care is taken to demonstrate the chiasmal cistern. The smaller tumours are unlikely to be detected by angiography.

The parasagittal tumours are important because of the difficulties of eradicating them, rather than difficulty of diagnosis. The degree of implication of the sagittal sinus by the meningioma is the main controlling factor. In some, the tumour is only lightly attached to the sinus wall, from which it may easily be detached, and with suitable treatment of the "raw" area, recurrence is unlikely. In others, the sinus is to a greater or lesser extent

involved in the tumour, and complete removal can only be carried out by excising that portion of the sinus. If the tumour lies in front of the Rolandic vein, which can then be spared, excision of the sinus can be carried out with little or no residual disabilities. But resection of the sinus at a more posterior level leads to severe vascular damage to the paracentral lobule on each side, and sometimes to even more widespread damage so that the patient may be left with a residual motor-sensory quadriplegia. In such cases, decision has to be made whether only a partial removal of the tumour is preferable, with inevitable recurrence but which may not occur for many years. Similar problems are posed by the cases in which the tumour has penetrated the falx, and this may occur when the sinus is still retrievable; penetration of the falx may escape detection at operation unless specially looked for by incising the falx and inspecting its other side. The technical problems of removal posed by the hyperostosis, the vascularity of the tumour, its sessile attachment, are neurosurgical ones and are not considered here, but they demand the most careful exercise of the surgeon's judgment (Olivecrona, 1947; Grant, 1947).

Meningiomas arising within the ventricles have received considerable attention in recent years. They are relatively rare and consequently the correct diagnosis may not be made, with fatal consequences; but if recognized total removal can be successfully carried out in many cases with satisfactory results. Abbott and Courville (1942) reviewed 50 recorded cases; the tumour lay in the left ventricle in 28 cases, in the right in 15, and in both in two. Other observers have also noted that the left ventricle is more frequently affected than the right. The tumours probably arise in the glomus of the choroid plexus, and by the time they give rise to symptoms have grown to a large smooth firm mass obliterating the ventricle to a varying degree. The tumour may send a process into the third ventricle (Jefferson and Jackson, 1935) but otherwise their removal through an incision in the cortex is not difficult. The chief localizing symptoms are related to the diffuse hemispherical damage which these tumours produce because of their strategic situation, namely sensor-motor hemiparesis, hemianopia and visual hallucinations; since the majority occur in the dominant hemisphere there may also be disturbance of reading and writing. Busch (1939) reports his experience in five patients, one of which died. He found only one leash of vessels entering the tumour, from the choroidal artery. Huang and Araki (1954) have encountered ten such cases, and describe certain angiographic characteristics,

which include enlargement of the anterior choroidal artery. Wall (1954) has also made a useful contribution to this subject.

In the posterior cranial fossa, meningiomas fall into three main groups according to their situation. Russell and Bucy (1953) have reviewed 182 recorded cases and 15 personal ones. They estimate that one in ten intracranial meningiomas arises in the posterior fossa, and that a similar proportion of all tumours occurring in the posterior fossa are meningiomas. Of 160 cases, in 46 the tumour arose from the tentorium, in 38 it lay in the cerebello-pontine angle and in 29 it arose from the clivus, from the basilar groove or from the margin of the foramen magnum. The tentorial and laterally placed tumours give rise to the clinical picture of a slowly growing lateral cerebellar mass; the tumour may extend through the tentorium in a dumb-bell shape, and thereby create further problems in diagnosis and removal. Those arising in the "angle" mimic an acoustic nerve tumour; preservation of vestibular function and absence of enlargement of the internal porus acusticus in correctly projected radiograms may give the clue to the correct diagnosis. Meningiomas spreading over the clivus and downwards to the foramen magnum usually produce evidence of pontine or medullary involvement and multiple lower cranial nerve palsies. Tumours in the last two groups may combine the characteristics of each if they are widespread, as may often happen. Removal of these tumours carries a high mortality rate and is often impossible owing to their inaccessibility, their size and extent, and the proximity of important vessels and of the pons and medulla. But decompression and partial removal sometimes leads to useful extension of life (Campbell and Whitfield, 1948). Cushing was unable to remove the tumour completely in his first case of posterior fossa meningioma, but the patient survived for over 22 years.

Recent reviews by surgeons of long experience (Grant, 1954; Horrax, 1952) shew that in spite of the advances in ancillary methods of diagnosis and in technique to aid the surgeon in his operation, meningiomas still provide great problems, and their removal, or attempted removal may carry a high mortality. The latter varies from 14 per cent to 30 per cent according to the type and situation of the tumour. Sound judgment needs to be exercised in deciding upon and planning single or multiple stage removals, or resting content with partial removal. Grant describes that in 128 cases of convexity tumour there were 14 incomplete removals with four subsequent deaths from recurrence: in 74 basal

tumours there were 18 incomplete removals, followed by seven deaths from recurrence, and in 17 posterior fossa tumours there were four incomplete removals and two deaths from recurrence. In Horrax's series, 78 per cent survived for 5-18 years, and of these 85 per cent were working or in good health.

Nerve Roots

A distinction is now drawn between the isolated encapsulated tumour which may occur on the posterior spinal roots, the acoustic nerve and occasionally the trigeminal and other cranial nerves, and the multiple nerve tumours of Von Recklinghausen's neurofibromatosis. The acoustic and other solitary nerve root tumours are regarded as arising from the cells of the sheath of Schwann, and the term schwannoma is preferred by some neuropathologists. A brief review of the various manifestations of von Recklinghausen's disease has been made by Robb-Smith and Pennybacker (1950).

Acoustic Schwannoma gives rise in the majority of cases to an easily recognized clinical picture. Cushing (1917) held that the correct diagnosis largely depends upon the accuracy of the chronological sequence of events. But Edwards and Patterson (1951) who have analysed the symptoms and signs in a large series of cases, point out that for the *early* diagnosis of these tumours, the pattern of evolution is of little help. Naturally, the diagnosis of the fully developed syndrome will receive greater aid from a study of sequence than is obtainable where the tumour is so small as to give rise only to minor inconvenience. They found that the initial symptom was referable to the acoustic nerve, and trigeminal symptoms arose later; these symptoms were present for about half the total duration of the illness before the next symptom—headache—developed. Early diagnosis must therefore make full use of the tests of disordered function of these two nerves. It has been the experience of most neuro-surgeons that patients suffering from these tumours are referred usually by neurologists, and rarely by aural surgeons. That is to say, the patients seek treatment because of the symptoms of raised intracranial pressure or of disabling ataxia, rather than as the result of eighth nerve disturbances, which they ignore or the nature of which is not recognized by aural examination. Olsen and Horrax (1944) found that nystagmus was present in all their patients, ataxia in 90 per cent and papilloedema in 76 per cent. Givré and Olivecrona (1949) have the same experience, and at operation the tumour was found to be a large one "almost without exception". Early

diagnosis is essential if the severity of the operation is to be considerably reduced, and will render possible the sparing of the facial nerve during removal of the tumour. In order to elucidate the causes of deafness, tests have been elaborated by Dix, Hallpike and Hood (1949) which are of great value. Fitzgerald and Hallpike (1942) have improved the methods of testing vestibular function; abolition or impairment of vestibular function is an almost constant accompaniment of acoustic nerve tumours. Elliott and McKissock (1954) give examples of successful diagnosis of early cases, and emphasize the need to search for the slight signs and to make full use of the modern methods of aural investigation.

In the early days of neuro-surgery, the removal of these tumours was attended by a prohibitive mortality of about 75 per cent. Cushing (1932) restricted the operation to an intra-capsular removal which he so perfected as to attain eventually a mortality of 3·4 per cent. His example was widely followed; the low immediate mortality and the avoidance of a facial paralysis were great achievements, and in many cases long survival occurred. But recurrence of the tumour and disability from inadequate relief of pressure on the pons were serious defects. Dandy (1934) re-introduced total removal of the tumour with various improvements in technique, and this is now the procedure of choice. The initial mortality is somewhat higher in the radical operation, and the facial nerve has normally to be sacrificed, but the ultimate rehabilitation is much better, and recurrence is avoided. Olivecrona (1940, Givré and Olivecrona, 1949) found that recurrence of a partially removed tumour occurred in 50 per cent of cases within a few years, and only 25 per cent of the patients undergoing partial removal were able to return to work, compared with 55 per cent in whom the tumour was completely removed. The details and results of surgical treatment have recently been published as a symposium by Horrax, Olivecrona, Pennybacker, Cairns and Northfield (1950).

Trigeminal Schwannoma is a much rarer tumour but with increasing knowledge of its natural history a correct diagnosis is now frequently made. The tumour may arise from the nerve behind the Gasserian ganglion, remaining entirely cerebello-pontine in its relationship, or it may spread into and through Meckel's cave and the ganglion, or it may arise primarily in the ganglion. The tumour may thus be dumb-bell-shaped and of great size, and careful clinical and ancillary examination will be necessary in order to detect its extent and to plan its removal. The

tumour is liable to be mistaken for an acoustic schwannoma, for in its later stages it will cause deafness by pressure on the acoustic nerve, as the latter tumours cause trigeminal disturbances. Early and marked cutaneous sensory loss in the trigeminal area, wasting and weakness of the masticatory muscles are characteristic features, and radiological examination of the skull may reveal the typical clean cut destruction of the apex of the petrous bone which when present is quite distinctive. Krayenbühl (1936) discussed two cases and the published records of 54 cases of primary tumour of the Gasserian ganglion and trigeminal root. He drew attention to the importance of trigeminal pain as a distinguishing feature of the ganglion tumours, and its absence when the tumour arises in the root.

Gliomas

Pathology. The classification of the tumours of neuroglial tissue on a basis of the morphology and of the embryological origin of the various glial cells was introduced by Bailey and Cushing in 1926. With some modifications it has been widely adopted but in recent years there has been an increasing tendency towards simplification. Willis (1948) considers it as unnecessarily complex, and implying histogenesis which is unwarranted. In his arguments he emphasizes that the three types of normal neuroglial cells—astrocytes, oligodendrocytes and ependymal cells—are not always distinct, and the tumours named after these cells are also not always “pure”; there may be a preponderance of one cell type, but mixed or transitional varieties are common. Many gliomas contain cells which are less well differentiated, more actively growing; these are anaplastic areas, degradation forms of the type tissue and are not tumours of embryonic cells. He deprecates the use of the suffix “blastoma” because it implies such an origin, the only occasion in which it is warranted being the medulloblastoma. It is a widely held view that the glioblastoma (spongioblastoma) multiforme commonly results from anaplasia in an astrocytoma. He draws attention again to Scherer’s writings (1938, 1940) wherein were described anaplastic foci, the rarity of “pure” astrocytoma, and the manner in which the pattern of the growth spread and the cell shape is often determined by the structure of the brain tissue in which the neoplasm has arisen. The simplified classification which has received much favour is that put forward by Cox (1933). Tumours of adult tissue; astrocytoma, oligodendroglioma, ependymoma and ganglioneuroma.

The anaplastic glioblastoma, and the transitional tumours, astroblastoma and spongioblastoma polare. Tumours of embryologically immature cells, medulloblastoma and medullo-epithelioma. Kernohan *et al.* (1949) have suggested further simplification by the application to gliomas of the Broders system of grading tumours according to the degree of malignancy as judged by cytology. Thus the glioblastoma becomes astrocytoma Grade 4, the medullo-epithelioma becomes ependymoma Grade 4, the oligodendroglioma has four grades and a new group is introduced, neuro-astrocytoma Grades 1-4 to cover the rare tumours of nerve cells. The medulloblastoma remains as such. Ringertz (1950) has also evolved a classification by grading, somewhat similar to that of the Mayo Clinic workers, but simpler, avoiding numerals and retaining the term glioblastoma. He defends this because of the difficulty in many specimens of deciding from what group the anaplastic growth is derived, and because it is by now a well recognized anaplastic glioma. The authors of both systems of grading have reviewed the case histories and survival rates, and it is clear that the histological diagnosis of "malignancy" broadly corresponds to the biological characters of the tumours. Thus for the purposes of prognosis in any individual case, the provision by the neuro-pathologist of a detailed report on the malignant characteristics of a glioma in addition to its "name" can be of the greatest value. Whether the tumour is classified by a number or by a name is of less importance; there is much to commend the retention of names which have come to denote well recognized entities, and nothing to be gained by the mere substitution of numbers for names.

Globus (1949, Globus and Cares 1953) remains a firm opponent to the proposed schemes of grading. He considers that grading is based on arbitrary and possibly deceptive standards, and maintains his belief in the histogenetic basis of tumour classification. In his view "every primary neuro-ectodermal tumour of brain contains a centre (or nucleus) varying in size and consisting of undifferentiated and hence potentially malignant cells". Thus the spongioblastoma multiforme arises from a cell-form of low grade differentiation, and this accounts for the rapid growth of the tumour. As has been indicated earlier, these opinions are not now held by the majority of neuropathologists.

Analyses of large series of cases of cerebral glioma reveal that males are more frequently affected than females, and the left hemisphere more frequently than the right. Penman and Smith

(1954) have confirmed this and also find that when due allowance is made for the relative volumes of the several lobes of the cerebrum, the temporal is the most common site. Ask-Upmark (1938) considered that gliomas of the parietal and temporal lobes together, far outnumbered those of the frontal lobe, though the surface area of the frontal lobe equalled the combined area of the parietal and temporal lobes. Ostertag (1952) thinks that there may be some correlation between the type of growth and its location in the brain, in the sense that the tumours of more primitive cell-type tend to occur in phylogenetically older parts of the brain. But these arguments are based on premises contrary to the views expressed earlier, that malignant changes occur by dedifferentiation of mature cells. Nevertheless, some biological factors as yet undiscovered must account for the curious predilections of gliomas.

Diagnosis and Treatment

Cerebrum. With the increased knowledge of the natural history—the biological behaviour—of gliomas, and of the possibilities and limitations of surgical treatment, it has become necessary to try and diagnose the nature of a cerebral tumour before planning treatment, in addition to its localization. There is need for an assessment of the type of glioma and not merely the differentiation between meningioma and glioma. The clinical course of the illness may often give a clue to the nature of the tumour and to cystic degeneration or to malignant changes. Thus an astrocytoma may give rise to a long and only slowly progressive history, but the rapid onset of signs of neurological deficit, and of raised intracranial pressure are highly suggestive of such changes. The formation of a large cyst often causes a more rapid deterioration than anaplasia. In elderly patients, the evolution of cerebral disturbance may be so rapid as to suggest cerebral thrombosis, and the common absence of evidence of raised intracranial pressure renders such a mistake easier. In addition the nature of the vascular supply to a glioblastoma makes it liable to episodes of hæmorrhage and of thrombosis, thus further mimicking cerebrovascular disease. A chronic subdural hæmatoma may present a picture indistinguishable from a rapidly growing malignant tumour (Petit-Dutaillis *et al.* 1953). Clinical methods will often enable a correct diagnosis to be made but cerebral angiography (described elsewhere) often provides the final and unequivocal answer. In some cases the diagnosis may remain in doubt, or a

decision is urgent and cannot be deferred. Diagnostic puncture through a suitably placed burr hole will immediately reveal a subdural hæmatoma, and if absent the suspected site of the tumour can be penetrated by a brain cannula, which may enter a cyst or unsuspected abscess. Aspiration will yield sufficient tissue for a rapid microscopic examination (Russell 1947, Morris 1947). This procedure is not without danger, because if the tumour is a vascular glioblastoma, hæmorrhage into it may occur with a fatal result. This risk is justifiable where one is seeking to exclude a remediable lesion, but needs explaining to relatives.

Treatment of gliomas of the cerebrum needs careful judgment, in order to assess the potentialities of surgery in the light of the situation of the tumour, its probable histological nature, and the risks of operation. The nature of the operation must also be decided. These are decisions for the neuro-surgeon to make, but the problems are of general interest. The assumption that certain cerebral gliomas—notably the astrocytoma—are benign, in the sense of their being entirely localized and therefore enucleable, has for the most part not been borne out in practice. Although very long survivals after excision have been reported (Eisenhardt 1937)—and sufficiently frequently and of sufficient duration to warrant operative removal, yet it is clear that many so-called benign tumours recur. This is now explained by Scherer's examinations of whole brain sections, in which say a "mural nodule" of astrocytoma is seen to extend histologically far beyond the macroscopic margin of the tumour. Portions of tumour unwittingly left *in situ* may later be the seat of anaplastic change. The difficulties—because of the variety of cell-type—of precise classification of a tumour only partly removed, have already been recounted. The present position of treatment can be summarized as follows. In cases diagnosed with certainty as glioblastoma, and in which the lesion has already produced such disabilities as hemiplegia and aphasia, operation is usually withheld. Where the tumour lies in a lobe in which extirpation can be practised without the risk of producing disability, many surgeons will advise operation, as a means of relieving raised intracranial pressure. When the inevitable recurrence occurs, the terminal illness is usually rapid, and often with little headache. This forms the "internal decompression" of McKenzie (1936). Some surgeons adopt the view that no case of glioblastoma should receive operation. This is a counsel of perfection, as such a tumour may be unexpectedly encountered in the course of a craniotomy; if the tumour is left untouched, the

operation is usually fatal. The more slowly growing, better differentiated gliomas—their nature can often be confirmed at operation by rapid microscopical examination—are usually explored, and a decision made in accordance with extent and situation. Some are conveniently placed for radical excision, others are more suitably dealt with conservatively, a decompression being provided to relieve pressure. Such patients survive many years if de-differentiation does not supervene. More detailed reviews of the surgery of gliomas have been given by Pennybacker (1950), Northfield (1950) and Northfield and Russell (1951).

Penman and Smith (1954) have made a detailed analysis of 296 cases of glioma; all aspects of the disease are considered, but only their observations on prognosis will be quoted. Of 162 patients with glioblastoma 133 were dead within a year, five lived for four years, and eight for periods from four to ten years. Of 95 patients with astrocytoma 52 died within a year, 13 lived for periods from four to ten years and four lived for more than ten years. Some of these patients died without active treatment. Among 84 patients who lived more than one year after treatment there were 52 whose survival was of a quality to which the term useful could be applied. These patients' tumours were distributed as follows; astrocytoma 32 (includes cerebellum) glioblastoma 16, oligodendroglioma three, medulloblastoma one.

Optic Nerves and Chiasma. A glioma may arise primarily in these structures, and by extension may invade the third ventricle. According to its site it will give rise to various abnormalities of the visual fields, often of a more bizarre pattern than those produced by chiasmal compression; disturbances of sexual and of general growth, signs of hypothalamic disorder and proptosis may occur. X-ray films of the skull may show no abnormality of the sella, or there may be an undercutting of the anterior clinoid process and enlargement of an optic foramen. The tumour is usually regarded as a form of astrocytoma. Hudson (1940) found that 90 per cent occurred in the first two decades. When the growth begins in an optic nerve, it may remain restricted to that structure for a considerable time and its excision is worth while. Such operations are better performed by transfrontal craniotomy and removal of the roof of the orbit; the whole length of the nerve from globe to chiasma can thereby be displayed. Survival for as long as 15 years after the removal of an optic nerve glioma has been reported (Neame, 1940)

Brain Stem. Several papers of interest have recently been

published concerning tumours involving the mid-brain, pons, and medulla. Barnett and Hyland (1952) reviewed 90 cases, of which 26 were intrinsic gliomas, 21 ependymomas, 10 pinealomas and 9 were papillomas. Hydrocephalic symptoms were common in the intraventricular and pineal tumours. Long-tract or cranial-nerve lesions—or both—were evident in two-thirds of the cases. Cooper, Kernohan and Craig (1952) found that in tumours of the medulla, vomiting and hiccup were frequent and that sudden death was a common termination. Cairns (1950) drew attention to the frequency with which mental symptoms may occur in patients suffering from pontine glioma. Although tumours in the cerebello-pontine angle are usually schwannomas or meningiomas, glioma may sometimes be found. These may arise from the neighbouring cerebellar tissue, but Kernohan *et al.* (1948) have shewn that they may arise from glial tissue normally present in the floor of the foramen of Luschka. They report ten cases; eight were of ependymoma, all large tumours and in six the patients died after operation and in the other two death occurred during observation. In two patients the tumour was an astrocytoma and both patients survived operative removal.

Cerebellum. The problems presented by gliomas of the cerebellum are less difficult than those of the cerebrum. The histological types are fewer and more constant, and the clinical syndrome is generally recognisable. The ependymoma and the astrocytoma are histologically benign and biologically prove to be so, provided their situation is such that they can be completely extirpated. In practice, the astrocytoma usually remains restricted to the lobes and vermis and can then be entirely removed, though occasionally this proves impossible, because of spread into the pons through the middle peduncle, or because of adhesions to the floor of the fourth ventricle. The large size of some of these tumours renders the operative mortality high. Grant (1950) reports a total mortality of 32 per cent although 25 recent consecutive patients were operated upon without fatality. Of 61 patients, 25 were still living at the time of his review, eight for over ten years. The cerebellar astrocytoma is in its biological behaviour quite different from the cerebral variety. The ependymoma is also histologically benign, but its situation often prevents its total removal. It lies within the fourth ventricle, and usually has an attachment of varying extent to the floor, particularly at the calamus scriptorius. The operation carries a high mortality, and if fragments of tumour remain undestroyed recurrence is likely—though this may be

deferred for many years. Fourth ventricle tumours often provide diagnostic problems because vomiting may be the only or the most prominent symptom for a long period of time.

The medulloblastoma is a highly malignant tumour occurring with much greater frequency in children than in adults. In a series of 168 cases reported by Swan (1944), 79 occurred in the first decade. In children the tumour is nearly always mid-line in situation, while in adults it is as often unilateral as central. The tumour is considered to arise from the foetal granular layer of Obersteiner or from primitive cell-rests in the posterior medullary velum; a study of these cell-rests has been carried out by Brzutowicz and Kernohan (1952). Although the tumour in adults is histologically indistinguishable from that in children, it runs a more benign course. Subarachnoid seeding may occur at all ages. In a series reported by Spitz, Shenkin and Grant (1947) 62 per cent of the adults survived for three or more years, but no patient under 16 years of age lived for longer than three and a half years. Penfield and Feindel (1947) have reported the case of an adult who lived for 17 years after treatment, before a recurrence led to her death. Medulloblastoma is radio-sensitive, but unfortunately the tumour sooner or later recurs and irradiation eventually fails. Surgical treatment is now normally limited to a decompressing operation and biopsy; if the obstructive hydrocephalus caused by the tumour has resulted in papilloedema so severe as to imperil eyesight, removal of sufficient tumour to enable C.S.F. to escape from the fourth ventricle is advisable. Radiotherapy to the whole neuraxis is instituted as soon as possible. The average period of survival in children is about three years; more detailed results can be found in the papers by Lampe and MacIntyre (1949) and Paterson and Farr (1953). Zuppperger and Krayenbühl (1948) have suggested that operative interference with the tumour itself (as distinct from decompression) may increase the liability to spinal dissemination.

Papillomas of the Choroid Plexus

These rare tumours may arise within any of the ventricles and at any age, though they are more frequent in children and about one half occur in the fourth ventricle. Histologically they resemble the choroid plexus and although the cells do not appear malignant the tumour may disseminate throughout the cerebrospinal fluid pathways. These tumours may be associated with considerable hydrocephalus, even when the situation of the tumour is such that

it cannot obstruct the flow of C.S.F. Thus, in Case 1 of Kahn and Luros (1952) ventriculograms revealed symmetrical and widely dilated lateral ventricles with a mass the size of a walnut in the glomus of the left lateral choroid plexus—a position in which it could not possibly cause hydrocephalus by obstruction. In this patient, after posterior fossa exploration had revealed no obstruction to the outflow of fluid into the cisterna magna, the choroid plexus papilloma was removed; all symptoms were relieved and the patient was well five years later. Other similar cases have been reported, and the writer has seen examples. Dilatation of the lateral ventricles with C.S.F. may theoretically be brought about by an over-production of C.S.F., by an obstruction to its outflow, or by a defect of absorption. That the first method can occur has until now never been satisfactorily proved clinically or experimentally and indeed Russell (1949) has described a necropsy specimen in which there was marked ventricular dilatation, fibrous thickening and cellular infiltration of the leptomeninges indicating a low grade meningitis, and a choroid plexus papilloma in one lateral ventricle. She ascribed the hydrocephalus to the meningeal fibrosis, and the papilloma was regarded as incidental. In a more recent contribution to the subject of hydrocephalus, Russell (1955) agrees that there is strong evidence in support of the contention that a papilloma may cause hydrocephalus by producing excessive quantities of C.S.F. though the precise mechanism remains obscure.

Colloid Cyst

This cyst has a constant situation, lying in the anterior part of the third ventricle and attached to the choroid plexus of its roof. The suggestion made by Sjövall (1909) that it may be derived from the paraphysis has recently been examined by Mosberg and Blackwood (1954) in a study of the histology and pathology of this moderately rare but important tumour. It may give rise to symptoms attributable to the obstructive hydrocephalus which it produces when it reaches an adequate size, and to disturbances of the hypothalamus by its expansion within the third ventricle. A variety of clinical pictures may be produced in which diverse manifestations predominate. Sudden and acute hydrocephalus may cause death in 24–48 hours, or chronic hydrocephalus may lead to dementia; raised intracranial pressure without localizing symptoms and signs may be remittent; such spontaneous remissions may be due to leakage of cyst contents through minute necroses in the cyst wall (McLean 1936). Jefferson and Jackson

(1939) have drawn attention to the sudden attacks of weakness of the legs which also occur in other forms of third ventricle tumour. Byrom and Russell (1932) described a case in which diabetes mellitus occurred, and in which the terminal coma was characterized by the absence of dehydration and its resistance to insulin. Severe glycosuria without ketosis may be seen with colloid cysts as with other cerebral lesions. The most recent and exhaustive paper on this subject appears to be that by Cairns and Mosberg (1951) who describe 19 personal cases and have found 142 cases in the literature. In this important paper the authors not only discuss diagnosis, treatment and the late results of operation, but also "consider the evidence which these cases afford on the function of those parts of the brain which lie adjacent to the cyst". Although the cyst is situated in such an apparently inaccessible part of the brain, operative removal is quite practicable; in Cairn's series the cyst was removed in 11 cases with two deaths.

Hæmangioblastoma

This tumour is largely cerebellar in situation, and its relationship to the angioblastic meningioma has been mentioned earlier. Although the tumour may appear buried in the cerebellum there is no doubt that many arise from the pia. Russell (1950) was able to trace a direct continuity between tumour and pia in 21 of 33 cases. But its participation in Lindau's syndrome, and its not infrequent familial incidence are strong arguments in favour of awarding it an identity of its own. A remarkable family is described by Tonning Warren and Barrie (1952); the mother probably transmitted the lesion, for an eye was removed at the age of 22, and she later died of a brain tumour; of the four children three are known to have Lindau's syndrome and each has had a hæmangioblastoma of the cerebellum, and the fourth has an angioma of an eyelid.

Olivecrona (1952) has recently reviewed his experience of 70 cases of cerebellar hæmangioblastoma. He finds that of posterior fossa tumours in adults they occupy fourth place, roughly as frequent as meningiomas but less common than gliomas and schwannomas. The great majority occurred in the lateral lobes, and he considers that cyst formation is not as common as is generally accepted. In 63 patients the tumour was removed with ten fatalities. Of those who survived the operation 42 are well and able to work. He draws attention to those cases in which there is a family history of the lesion, for in all these (three in his series) new tumours appeared later. Recurrence occurred in two other

cases, but it is uncertain whether these were due to incomplete removal of the original tumour, or whether they were separate tumours. It has long been the general opinion that when removal of a cerebellar hæmangioblastoma is complete a recurrence will not occur. But doubt is now being cast upon this belief. Cramer and Hinsey (1952) report that in 53 patients there was recurrence in 11, and Pennybacker (1954) describes similar experiences and in some the recurrence was quite clearly at the site of the original tumour. In one case the tumour recurred a third time and then invaded dura mater and muscle; histologically the tumour was identical with the primary one removed 19 years previously. Cramer and Hinsey draw attention to the finding of polycythæmia in some of their patients; this was the case only in the non-cystic vascular tumours. The cause is not clear, and they offer as alternative suggestions that the tumour tissue may be erythroblastic, or that it acts by providing an arterio-venous shunt.

Pineal Tumours

Although the pineal body may occasionally be the site of a glioma, the commonly occurring tumour is a pinealoma. This name was chosen because the tumour was originally regarded as being derived from pineal cells in an early stage of development. But Russell (1944) has produced evidence that the majority of these tumours should be regarded as atypical teratomas, and points out their close histological resemblance to seminoma of the testis and dysgerminoma of the ovary. It is accepted that a true pinealoma—i.e., arising from pineal cells—may be encountered, but that it is uncommon. McGovern (1949) considers that there are two varieties: the pinealoblastoma, an undifferentiated tumour, and the pinealocytoma of more mature cells.

Pineal tumours produce symptoms due to hydrocephalus, the result of their obstructing the posterior extremity of the third ventricle and the iter. Compression of the quadrigeminal plate commonly occurs giving rise to the localizing signs of abnormality of the pupils and of the ocular movements, and ptosis. Other symptoms may sometimes be encountered, due to disturbances of the hypothalamic mechanisms; of these diabetes insipidus and precocious puberty are the most common. Russell and Sachs (1943) have analysed the records of 58 cases of pinealoma; diabetes insipidus occurred in 15, and of the 17 patients who were not more than 15 years of age three had developed pubertas præcox. Whether these effects upon the vegetative nervous centres may be

brought about solely by hydrocephalic distension of the third ventricle is uncertain. In some, perhaps many cases it is due to invasion by tumour. Horrax and Wyatt (1947) have described three cases of so-called "ectopic" pinealoma in the chiasmal region. In one the tumour reached that situation by direct invasion from a pineal tumour; in another a pineal tumour had previously been removed and the ectopic growth was probably due to ventricular transplantation. In a review of the diverse manifestations of hypothalamic disease, Bauer (1954) has found 60 cases with necropsy records in the literature. Pubertas præcox was present in 24 and in all these the pituitary gland was normal; the commonest lesion was a glioma of the hypothalamus, and a pineal metastasis was present in one; other lesions found at post mortem examination were congenital hyperplasia, inflammation and tuberous sclerosis. In no case of pubertas præcox was a Rathke-pouch tumour found.

Surgical extirpation was at one time considered to be the only treatment offering the prospects of cure. But this operation carries a high mortality rate and the tumour frequently recurs. Rand and Lemmer (1953) report a mortality of 70 per cent in 16 patients, and one survives after 11 years. The commonly accepted procedure at present is a subtemporal decompression or a short circuiting operation, either an anterior third ventriculostomy or a ventriculo-cisternostomy (Torkildsen 1948), followed by irradiation. Rand and Lemmer report survivals up to 11 years, and Horrax and Daniels (1942) up to eight years by such methods.

Adenomas of the Pituitary Gland

Considerable attention has been paid in recent years to the gross pathological anatomy of pituitary adenomas; they may grow to such a size that they extend far beyond the boundaries of the sella turcica. An accurate assessment of size and of direction of spread is essential for the success of any operation, the choice of which may be influenced by such information. Jefferson has been particularly interested in these "Extrasellar Extensions of Pituitary Adenomas" (1940) and for those florid examples which may spread into the cavernous sinus and even into Meckel's cave he uses the word malignant, because of their invasiveness though not in a cytological sense, Willis (1948) regards them in the same light. Operation in this kind of tumour carries a heavy mortality; in Jefferson's series 33 per cent, as compared with 2 per cent in the

case of average sized tumours. Massive tumours may be suspected in cases with a long history, severe visual failure, mental retardation, epilepsy and occasionally papilloedema; the radiological demonstration of enlargement of the optic foramina and of the superior orbital fissures is highly suggestive. Extension of the tumour into the cavernous sinus is likely to interfere with one or more of the ocular motor nerves or the trigeminus, sometimes causing proptosis and lid oedema. Weinberger, Adler and Grant (1940) encountered 14 such cases in a series of 169 patients with pituitary adenoma. In two there was no enlargement of the sella turcica, and in six vision was unaffected. Love (1952) found a normal sella in 12 of 314 cases. Air encephalography is being used with increasing frequency to outline the extent of these and of other supra-sellar masses, but it is not without its risk; angiography may also provide similar information.

Detailed knowledge of the local anatomy is important in another respect. The position of the optic chiasma relative to the sella turcica varies; it is commonly situated about 10mm above the diaphragma, and slightly anterior to the coronal plane of the posterior clinoid processes. In about 5 per cent of specimens the optic nerves are so short that the chiasma lies on a plane anterior to the mouth of the sella (prefixed) and in 4 per cent it lies posterior to the dorsum sellæ (Schaeffer 1924). According to the position of the chiasma, the protruding adenoma may come to lie in front of, behind, or to one side of the chiasma (when the adenoma emerges from the sella asymmetrically), with consequent variation in the pattern of visual field defect. Henderson (1939) and McConnell and Mooney (1938) have made valuable contributions to the interpretation of these visual field defects. Choice of operation is important in these cases, for adequate access to the tumour by a frontal craniotomy may be denied if a prefixed chiasma is present, and a transphenoidal operation may be necessary.

Spontaneous hæmorrhage may occasionally occur in a pituitary adenoma and if severe it is rapidly fatal. The condition mimics that of a ruptured aneurysm, and death occurs either from the consequent damage to the neighbouring vegetative centres or by reason of pituitary-adrenal failure. Müller and Pia (1953) describe 19 cases in which hæmorrhage had occurred either as a recent apoplectiform event or in which the operative findings were suggestive. They have found 58 cases reported in the literature. These authors consider that in acute cases immediate operation is advisable, in association with supportive hormonal treatment.

Brougham, Heusner and Adams (1950) and List, Williams and Balyeat (1952) adopt a more conservative attitude.

A considerable stimulus to the study of patients with pituitary adenomas—and other tumours in this vicinity—has been provided by recent advances in endocrinology. In particular the notable contributions by Sheehan and his co-workers on Simmonds disease have helped in the clinical assessment of the systemic effects of atrophy of the gland. The treatment of depressed pituitary function in Simmonds disease may have a direct application in the treatment of patients with pituitary functions disturbed by tumours. This is especially so in the cases in which operative treatment is undertaken. One of the factors which may influence the course of operation is the degree of derangement of the pituitary—adrenal function, though it is likely that other intrinsic pituitary disturbances occur which are as yet ill understood. Investigation of a case of pituitary adenoma must therefore include an evaluation of endocrine and in particular of adrenal function. Nurnberger and Korey (1953) have recently recorded the results of an intensive study along these lines, in a series of 117 patients with chromophobe adenoma, and append a large bibliography. Prunty (1950, 1954) and Smart (1954) provide concise reviews of the generally accepted methods of assessing pituitary and adrenal cortical activity. Laboratory techniques however, must not be allowed to supercede a critical clinical examination of symptoms and signs which may give clues to the extent of damage of the anterior pituitary. It is uncommon to find in cases of pituitary adenoma a severe degree of panhypopituitarism, probably because the gland is so slowly compressed, and enlargement of the sella turcica continues to provide some room for it. Sheehan and Summers (1949) have shewn that even as small a fraction of the gland as one quarter is sufficient to maintain some endocrine activity. Infarction produces greater destruction than slow compression, in which the blood supply probably remains intact unless and until damaged by operative interference. A few observations on the weights of adrenal glands found at necropsy in patients dying after an operation for pituitary adenoma suggest that they rarely fall below the critical level suggested by Sheehan. (Northfield 1955). A notable difference between patients with Simmonds disease and those who have had an operation for pituitary adenoma is that the latter rarely suffer from progressive pituitary failure, and recurrent episodes of partial failure in response to infection etc. are practically unknown. Although return of gonadal activity

is rare, physical vigour is usually good after recovery from operation. It is likely that the remnants of the gland regenerate to some extent after their compression is relieved. One is reminded of the experiments described by Harris (1951) which demonstrated the facility with which hypophysial portal vessels regenerate after stalk section, and so prevent gonadal atrophy; this only occurred if the cut ends of the pituitary stalk were insulated from one another by a piece of paper.

The extent to which adrenal failure is a factor in the mortality of operations for pituitary adenoma is undetermined. Reports have appeared of cases in which it appeared to be so (Houghton 1953, Caughey, James and Macleod 1952) but the manner of death and the necropsy findings suggest that damage to vital centres by hæmorrhage, trauma or cerebral compression is the more common explanation (Northfield 1955). Grant (1948) mentions that amongst 71 adenomas—in which there were eight deaths—necropsy revealed adrenal atrophy in two, and suggested that hormone treatment might be helpful. Love (1952) gives cortisone as a routine during the period of operation, but admits he does not know if it is of value. Petit-Dutaillis *et al.* (1953) discuss the subject in reporting three cases illustrating the dangers of operation on big tumours, in which cortisone was given but the operations terminated fatally.

A transfrontal approach to the tumour is the method of choice in most patients, the indication for operation (except in cases of basophilism) being pressure on neighbouring structures, and the visual pathways are of course the most commonly affected. Occasionally, when vision in one eye has been nearly or completely destroyed, access may be improved and a better operation made possible by dividing that optic nerve, and this should be foreseen and permission obtained. The transphenoidal operation may be chosen in cases in which a prefixed chiasma is suspected, or if vision is severely affected, for manipulations around the tenuous optic nerves may destroy their greatly diminished conductive powers (Cairns 1936). The results of the transphenoidal operation have been given by Hirsch (1948) who has had considerable experience with it, and Naffziger (1952) still makes use of it. Naffziger, Love, and Grant (1948) have each reviewed their experiences, and Bakay (1950) has given a detailed account of 300 cases of operation from Olivecrona's clinic, including late results; in 28 patients who died, pituitary insufficiency is cited as the cause in only four. Henderson's (1939) review of the later results

of Cushing's cases still provides a unique contribution to this subject.

The place of irradiation in the treatment of pituitary adenomas is a matter of opinion, though its value in some respects can no longer be doubted. Henderson (1939) shewed that post-operative irradiation diminishes the risk of recurrence of the tumour. In acromegaly when the tumour has caused little or no disturbance of vision, and in some cases of basophilism, common clinical experience has shewn its value. But it is in the treatment of the chromophobe adenoma, as an alternative to operation, that difference of opinion arises. Claims that these tumours are diminished in size by irradiation are seldom substantiated by the publication of the visual fields, on which ground the value of the treatment must stand or fall. Evans and Picciotto (1948) make a factual report of seven cases treated the results were good in three. Good results are also claimed by Kerr and Cooper (1942) and Davidoff and Feiring (1948). 'A safe course to adopt is to recommend irradiation in tumours which have produced only minor defects of the visual fields and to recommend operation if the fields do not expand to normal within a few months. As Grant says, there is danger that irradiation may induce in the surgeon a false sense of security, and recommends that any rule should be rigidly adhered to, so as to avoid procrastination. Radon implantation in cases of basophilism has been employed in a few cases with some measure of success (Pattison and Swan 1938, Northfield 1949) but partial adrenalectomy may prove a better form of treatment.

Rathke-Pouch Tumours

Synonyms for these tumours are craniopharyngioma, suprasellar cyst, epidermoid and adamantinoma and they arise from remnants of Rathke's pouch of buccal epithelium. Occasionally such a tumour arises within the sella, causing it to become ballooned like a pituitary adenoma; the common site is above the sella along the infundibulum, and a few arise in the region of the tuber. In Dott's series (1938) there were four tuberal in a total of 28. The solid portions of the tumour contain trabeculae of epithelium resembling the adamantinoma of the jaw. Sprawson (1937) doubted whether the latter tumour, except in a small minority of cases, ever arose from dental epithelium; he regards both tumours as basal-celled carcinoma. Willis points out how these tumours may invade adjacent tissue e.g., the brain, and it is a common experience to

find such tumours intimately blended with the floor and the walls of the third ventricle, prohibiting their successful removal.

The symptoms of these tumours are now well known, and they group themselves in accordance with their site of origin. The age at which the epithelial remnant takes on active growth also influences the clinical pattern which emerges. Gordy, Peet and Kahn (1949) record in their series the case of a patient aged 65 years, in whom there were no disturbances of growth or of other endocrine systems; over half of their cases occurred in the first two decades of life. Love and Marshall (1950) have reported 100 cases, ages ranging from 3–67 years, and 34 were in the second decade. Visual failure was a first symptom in 25, and was present in 82. Papilloedema occurred in 28, and visual field disturbances either bitemporal or homonymous in 64. Endocrine disturbances were found in 55 cases; the various manifestations are analysed. In the younger patients hydrocephalic symptoms are particularly common, and headache occurred in 88 and vomiting in 41. In a group of 16 children Ingraham and Scott (1946) report that headache and vomiting were the first symptom in all but one. In five patients physical growth had been arrested, and in three there was diabetes insipidus.

The treatment of the majority of these tumours still remains disappointing. A few—those which are predominantly intrasellar and small ones suprasellar in situation but which have not yet become adherent to the base of the brain—may be successfully completely removed. Gordy, Peet and Kahn think that total extirpation is only likely to be feasible in young children while the tumour is still small; but often it happens that symptoms do not develop until the tumour is already of unmanageable size. In the great majority of cases the tumour has already acquired attachments to the third ventricle, and such attachments are not light adhesions but are structurally firm connections, as described by Willis. Cushing's mortality was 21·8 per cent, and Davidoff (1940) reported that of the 23 such patients which Cushing operated upon in the period 1924–37, only four were alive 7–11 years later. Love and Marshall report a mortality of approximately 40 per cent, and five patients survived ten or more years. In face of the high mortality and the essentially irremovable nature of Rathke-pouch tumours, surgeons are becoming more conservative and applying palliative measures. It is known that some patients may live for many years, partially incapacitated by such a tumour, without operative interference. If the hydrocephalus be relieved by a

by-passing operation such as that of Torkildsen then the term of life preserved may often be happy and useful, even if blindness results from unrelieved chiasmal pressure. Whether the use of corticotrophin and of cortisone will diminish the operative risk in these patients has yet to be proved. Post-mortem studies give little encouragement, for death is usually quite adequately explained by the local morbid changes resulting from the trauma of operation (Northfield 1955). Ingraham, Matson and McLaurin (1952) have described some cases in which endocrine treatment was used during the operative period, but there is little evidence that cases so treated carried a lower mortality than their previous series (Ingraham and Scott 1946).

X-ray treatment of these tumours seems of doubtful benefit, though Love and Marshall believe that it is helpful. But irradiation has been applied by a different method. Klar (1953) describes a procedure whereby he punctures the cyst through a small burr-hole and inserts radio-active phosphorous. It is likely that for the repeated emptying of cysts, when their situation has been determined either by operation or by ventriculography, stereotaxic methods will prove very useful.

Metastatic Tumours

It might be thought that if an intracranial tumour can be shewn with reasonable certainty to be metastatic, treatment can only be symptomatic. Experience has shewn that this is not necessarily so, and that in a few cases operative treatment is well worth while. If the primary growth is operable, or if it has already been removed, and if the metastasis can be shewn to be solitary, its removal may be followed by some years of useful life. The clinical picture may indicate whether the lesion is likely to be single or multiple, and angiography is frequently of great help in deciding this point. The duration of cerebral symptoms is also of some assistance; prognosis is poor when this is short, but where the duration is over three months operation is more likely to be useful (Livingstone, Horrax and Sachs, 1948). In Olivecrona's clinic, the erythrocyte sedimentation rate has been found of value, the high figures being usually associated with multiplicity (Störtebecker, 1954). Although the brain may be the seat of metastases from any primary site, the lung the kidney and the breast are the commonest. Necropsy studies shew that the metastasis is solitary in about one third of the cases of cerebral secondary growths, (Globus and Meltzer, 1942) and Störtebecker reported that in one fifth there

were no other metastases in the body. The latter's paper gives an extensive review of the results of operation, and confirms that with careful selection operation can be beneficial. Flavell (1949) reported a case of a pulmonary carcinoma with a cerebral metastasis; both tumours were removed, and although the cerebral growth was adherent to the dura mater, this patient is still alive and well, earning his living seven years later.

Radiotherapy

Although X-ray treatment is commonly administered to patients suffering from glioma, and by many as the treatment of choice in cases of glioblastoma, its value is for the most part difficult to evaluate. Clinical experience offers indisputable evidence that a medulloblastoma is remarkably radiosensitive. The effect of treatment can be easily assessed, because the clinical picture, age incidence, tumour site and histology are all fairly constant and consequently the progress of one patient can easily be compared with that of others. But experience has also taught us that the tumour recurs, and that recurrences are radio-resistant, so that sooner or later the patient dies of the disease. Attempts have been made to study the problem of radio-sensitivity by histological examination of the tumour; the results have not been of much assistance because of the wide range of natural variation in the histological structure of gliomas, and because of the complicating factor of the operation. Davis and Weil (1937) and Tarlov (1937) considered that only in the medulloblastoma could changes be detected which were indisputably due to irradiation. Pennybacker (1946) found that the survival rate of patients with glioblastoma was longer if radiotherapy were given than if withheld, and in one case dying seven years after treatment no tumour could be detected at the necropsy (Pennybacker and Russell, 1948). The effects of irradiation upon experimentally induced gliomas in animals provides an opportunity for more accurate assessment of the effects of X-ray treatment. Tansley and Wilson (1947) found that cellular damage undoubtedly occurred, but not every tumour was affected, and there were no complete cures. Radiotherapy is sometimes given to other intracranial tumours when for one reason or another they cannot be entirely removed surgically. Some meningiomas and hæmangioblastomas appear to be radio-sensitive (McWhirter, 1946) and as mentioned earlier certain cases of pituitary adenoma can be successfully treated.

Advances in the techniques of radiotherapy aim at increasing the tumour-dose with minimum irradiation of the surrounding tissues. For this purpose the source of irradiation is being greatly increased in power, by the introduction of high-voltage X-ray apparatus (Layne *et al.* 1953) and of radio-active cobalt. The results of these methods will be awaited with keen interest, and in particular the possibility of reducing the risk of damage to surrounding tissue. Numerous reports now make it clear that healthy brain may be severely damaged by irradiation, and so extensively that it may be fatal. How frequently this may occur is unknown, for there is usually a latent period of a year or more after treatment before radio-necrosis manifests itself; when this happens the symptoms and signs are often similar to those to be anticipated by a recurrence of the tumour and this diagnosis is commonly made. Sometimes the induced lesion may be at a distance from the tumour irradiated, which may have been outside the brain, and in such cases the diagnosis of radio-necrosis can be made on clinical grounds with some certainty (Boden, 1949, 1950). The morbid anatomy of radionecrosis of the brain has been fully described by Pennybacker and Russell (1948) who considered that the pathological changes might have been brought about as a result of vascular disturbances. Intense changes in the blood vessels and widespread infiltration of the area involved with fibrin filaments were characteristic of radionecrosis. Russell, Wilson and Tansley (1949) have carried out experiments on the brains of rabbits, and have been able to produce similar lesions by X-rays. Their experiments strengthen the view that the chief damage is upon the blood vessels, increasing their capillary permeability and leading to degenerative changes in the walls of the vessels. Recent work by Clemente and Holst (1954) suggests that variations in the dose of X-rays may alter the character of the microscopic picture; with high doses vascular damage predominated, but lower doses appeared to select the parenchyma. There is a big field for research here, with an urgent and practical application.

Tuberculoma

Tuberculomas have become increasingly rare in this country, but are still occasionally encountered and usually during a craniotomy for a suspected neoplasm. They are relatively common in some countries and the introduction of streptomycin has revolutionized the results of operative treatment. Formerly, removal of the tuberculoma was usually followed by a fatal tuberculous

meningitis. Descuns, Garré and Phéline (1954) relate that before the use of streptomycin they had operated on ten patients and eight died; since using it approximately one half of the patients have survived. They found electroencephalography of some aid in diagnosis because of focal abnormalities with much spike activity; they avoid ventriculography because the tuberculous encephalitis may be aggravated, and prefer angiography. Their patients, mainly natives of North Africa, were mostly very ill, in poor condition and with large lesions. Asenjo *et. al.* (1951) have reviewed their large experience of 159 cases, of which 97 were verified histologically; in 64 the tuberculoma was single, and in the other 33 there was more than one lesion in the brain. Calcification was rarely encountered. In 86 cases it was possible to demonstrate a tuberculous lesion elsewhere in the body, being pulmonary or pleural in 62. That an active pulmonary lesion is not an invariable accompaniment was shown by the necropsies in 49 cases, for in seven the lungs were normal. In 67 patients no operation was carried out, and 22 died; in each of these necropsy verified the diagnosis. In the other cases, before streptomycin became available, operations were mostly limited to decompression, and in cases of brain stem tuberculoma, to by-passing operations to relieve the obstructive hydrocephalus. Complete removal of a tuberculoma was carried out in six patients but only one survived. Approximately one half of all cases operated upon, died. Since the introduction of streptomycin (and P.A.S.) there have been ten operations (up to the end of 1949) and only two patients have died.

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